CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

STATISTICAL REVIEW(S)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-856/N0046
Name of drug:	Uloric (febuxostat)
Indication:	Management of hyperuricemia in patients with gout
Applicant:	Tap Pharmaceuticals
Dates:	Letter July 18, 2008; PDUFA January 18, 2009
Review priority:	P
Biometrics division:	Division of Biometrics II
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Keywords: NDA review, clinical studies

TABLE OF CONTENTS

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The Applicant, Tap Pharmaceutical Product, Inc. seeks to market Uloric (febuxostat) 40 mg and 80 mg once daily (QD) for the management of hyperuricemia in patients with gout.

The evidence taken collectively from studies reviewed indicated statistical support in favor of febuxostat 80 mg QD in reducing serum urate levels in subjects with gout. There is also evidence supporting the febuxostat 80 mg QD dose in patients with mild-to-moderate renal impairment.

There is some evidence that febuxostat 40 mg QD, although not superior, is effective in reducing serum urate level in patients with gout.

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Based on the analysis of primary endpoint by week, there is evidence that reduction in serum uric acid level to less than 6.0 mg per dL was noted in some patients by the Week 2 visit and was maintained throughout treatment.

In terms of safety, based on the information collected thus far, there are still uncertainties with regard to cardiovascular safety of febuxostat. Numerically, a slightly higher proportion of subjects treated with febuxostat with adjudicated cardiovascular event identified using the Antiplatelet Trialists' Collaboration (APTC) criteria. Although the new study suggests no difference in risk between febuxostat and allopurinol, there is a lingering clinical question whether these studies produced sufficient number of events to adequately address cardiovascular risk. There is also a question with regards to the duration of exposure, particularly in the allopurinol arm. Thus, I recommend that the Applicant conduct an outcome study as part of their Phase 4 commitment to adequately address the cardiovascular safety signal or other potential safety risk of febuxostat.

An advisory committee meeting was held last November 24, 2008 to discuss this application with the Arthritis Advisory Committee (AAC) members. The Division submitted four questions to the AAC for discussion. The questions include the safety of febuxostat, appropriate dosing, special population, and the committee's recommendation of whether to approve febuxostat for the treatment of chronic gout and what additional studies should be conducted post-approval to further assess the safety of the product. Although the advisory committee members expressed concerns about cardiovascular safety of febuxostat, they voted 12 to 0 (one absention) to approve both the 40 mg QD and 80 mg QD doses of febuxostat. The committee members were convinced that there is a need for a new medication to treat gout, in part because some patients are intolerant of the current therapies (e.g. allopurinol) and in part because gout is treated suboptimally even when current therapies are appropriate. The advisory committee members also recommended that there should be an extensive post-marketing study to monitor safety. The design of the study was discussed (i.e. outcome study or observational study) but no consensus was reached.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The document submitted by the Applicant seeks to provide a complete response to each of the items identified by the Agency in the 02 August 2006 Approvable Letter for febuxostat NDA 21-856. This submission includes report from the new Phase 3 study (F-GT06-153), a 6-month, randomized-controlled study to evaluate the safety and efficacy of febuxostat 40 mg, febuxostat 80 mg, and allopurinol 300/200 (based on renal function) in the treatment of subjects with hyperuricemia and gout. This new study was designed to prospectively evaluate and adjudicate in a blinded fashion the APTC and non-APTC CV events by an independent committee of cardiovascular endpoints experts (2 cardiologists and 1 neurologist). The Applicant also includes reports from the two completed long-term extension studies (TMX-01-005 and C02-021), which provide an additional 12 months of exposure.

1.3 STATISTICAL ISSUES AND FINDINGS

During my review of the submission, I identified some issues that warranted further consideration both on efficacy and safety analyses, and I identified some issues that could be resolved by recoding and re-analyzing the data. I also identified various discrepancies between the raw and derived datasets. Reasons for most of these discrepancies were found not to affect the overall conclusion.

In the efficacy part, two statistical issues were noted. One is on the potential multiplicity problem associated with the change in the definition of the primary endpoint in the two old Phase 3 studies. Another is on the Applicant's approach in handling missing data due to patient dropout (i.e. using last observed value) instead of applying non-responder status to these patients. As noted in the review, the results from the analyses of the primary endpoint in Studies C02-009 and C02-010 were highly significant ($p<0.0001$) that applying multiplicity adjustment (e.g. Bonferroni) is not likely to change the overall conclusion. Furthermore, when applying a 'non-responder' status to patient who discontinued in all Phase 3 studies also did not alter the overall conclusion. The Applicant also

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In terms of safety, there are still uncertainties with regard to cardiovascular safety of febuxostat. Safety data were presented in the original submission, but due to the Division's concern on cardiovascular risk of febuxostat, the Applicant re-analyzed their safety data and applied APTC criteria to the cardiovascular data. One statistical issue with the analyses of safety data in the second cycle (2006) is that the application of APTC criteria and adjudication was introduced in a post hoc fashion. Thus, the analyses were performed post-hoc. As an example, in the two original Phase 3 studies, there were at least 20% of subjects discontinued from reasons other than adverse events or gout flare. This information is relevant since these subjects may have CV events that were not captured because they were not in the study and at that time, cardiovascular events are not judiciously reported. According to the Applicant, these patients are only followed for 30 days after they discontinued. Furthermore, not all the subjects adjudicated have severe cardiovascular adverse events, and not all subjects with severe cardiovascular events were adjudicated. One clinical issue is the small number of events. Patients with gout are expected to be older and have a greater risk for cardiovascular events. The fact that only small numbers of events were recorded produces some uncertainties about whether the findings definitely represented an increased risk of cardiovascular thromboembolic events with febuxostat. Like the short-term Phase 3 trials, there are also problems with the long-term studies. In these studies, subjects were allowed to switch doses or treatments based on serum urate level, AEs, or at the investigator's discretion over the entire length of treatment

in Study C02-021 and between Weeks 4 to 24 in Study TMX-01005. The number of subjects and the extent of exposure in the allopurinol group are smaller (almost 15 to 1) compared to the febuxostat group. The studies are also not complete at the time of the safety update.

In the 2008 submission, new data from Study FGT06153 and from the long-term studies were collected. The results were slightly different from the previous trials. More deaths were observed in the allopurinol arm compared to the febuxostat arm. There were also more investigator-reported primary APCT events in the allopurinol arm compared to the febuxostat arm. Numerically, there is no difference in the number of adjudicated APTC event between febuxostat and allopurinol in this new study. When I combined all the information from all Phase 3 randomized controlled studies, the differences between febuxostat and allopurinol are comparable suggesting no evidence in cardiovascular risk. The overall rate of mortality and cardiovascular mortality were comparable in both treatment groups, and so are the overall proportion of investigator-reported primary APTC and adjudicated APTC events. Although the difference in risk is small (suggesting no difference in risks), the confidence intervals are wide suggesting uncertainties in the estimated treatment effect. Clearly, there could still be a possibility of an excess cardiovascular risk with febuxostat compared to allopurinol.

If we think of Studies C02-009 and C02-010 as an interim look, then the addition of information from Study FGT06-153 can be considered the second interim look. The question is whether this new study FGT06153 can be considered the final look in the study of cardiovascular events or do we need more data to understand the cardiovascular signal of febuxostat. If the objective of Study FGT06-153 was to confirm the cardiovascular safety signal of febuxostat, then this study did not satisfy that objective.

In the long-term studies, the overall rate of mortality and cardiovascular mortality, as well as the overall proportion of investigator-reported primary APTC and adjudicated APTC events were not increased from the 2006 to the 2008 submissions suggesting events occur early in the trial than later.

2 INTRODUCTION

2.1 OVERVIEW

The Applicant, Tap Pharmaceutical Product, Inc. seeks to market Uloric (febuxostat) 40 mg and 80 mg once daily (QD) for the management of hyperuricemia in patients with gout.

In the original submission dated December 14, 2004, the Applicant included reports of two double-blind Phase 3 studies namely, Study #C02-009 and Study #C02-010, and one Phase 2 (Study #C TMX-00-004). The Applicant also submitted an interim report of an open-label safety extension of Studies #C02-009 and #C02-010 under Study #C02-021, since at the time of the submission, this study was still ongoing. The length of Study #C02-009 was 28 weeks and that of Study #C02-010 was 52 weeks. The objectives of these studies were to compare the safety and efficacy of selected doses of febuxostat to allopurinol and placebo for the treatment of subjects with gout. The efficacy results from all these studies were reviewed by Mohammad Atiar Rahman, Ph.D., a mathematical statistician within the Office of Biostatistics and Joel Schiffenbauer, M.D. of the Division of Anesthesia, Analgesia and Rheumatology Products. Meanwhile, the safety data were reviewed by Tatiana Oussova, M.D. of the same division. An approvable letter was issued on October 14, 2005.

One of the requirements was to "further evaluate the safety profile of Uloric, especially in regard to its potential to result in cardiovascular adverse events."
The Applicant submitted a complete response to the approvable letter from the initial review cycle on February 17, 2006 (serial no. 033). In that letter, they addressed the issue raised regarding the potential for febuxostat to increase the risk of cardiovascular/thrombotic adverse events. This was done by reanalyses of existing data that includes an adjudication of cardiovascular adverse events performed by a cardiologist Dr. White, in a blinded manner, and additional analyses of new data derived from ongoing long-term extension studies that factored differences in exposure between treatment groups into analysis. No new efficacy data was submitted during this cycle. No statistical review was conducted. The report from the reanalysis of the safety data was reviewed by Tatiana Oussova, M.D. and a secondary review was completed by Joel Schiffenbauer, M.D. The complete response did not adequately address the cardiovascular safety concerns noted during the first review cycle for the application, thus an approvable letter was issued to the Applicant. The following is one item listed in the August 2, 2006 approvable letter:

> Provide further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat in order to assure us that a dose level(s) with favorable risk-benefit characteristics has been defined.

The document currently submitted by the Applicant seeks to provide a complete response to each of the items identified by the Agency in the August 2, 2006 Approvable Letter for febuxostat NDA 21-856. This includes reports for the new Phase 3 study (F-GT06-153) and Phase 1 warfarin interaction study (F-P107-162), as well as the final clinical study reports for the long-term extension studies (C02-021 and TMX-01-005). An updated Integrated Summary of Safety (ISS) is provided as well as an updated benefit-risk assessment of febuxostat for the management of hyperuricemia in patients with gout.

2.2 DATA SOURCES

The electronic submission of this NDA can be found at:
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3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 DESIGN AND ANALYSIS PLAN

The clinical program comprised three Phase 3, double-blind, placebo-controlled studies (F-GT06-153, C02-009 and C02-010), a Phase 2 placebo-controlled study (TMX-00-004) and two long-term extension studies (Phase 2 study TMX-01-005 and Phase 3 study C02-21). The objective of the clinical development program is to demonstrate the safety and efficacy of febuxostat for the indication of the management of hyperuricemia in patients with gout. Table 1 summarizes the key elements of the study designs for the Phase 2 and 3 studies.

Table 1: Overview of Clinical Efficacy Studies

Study	Treatment Groups	Design	N[a]	Duration of Treatment/ Duration of Gout Flare Prophylaxis During Treatment	Study Population	Primary Efficacy Endpoint	Safety Assessments[g]
F-GT06-153	Fbx 40 mg QD and 80 mg QD; Allo 300/200 mg QD[b]	Randomized, double-blind, multicenter, active-controlled	2269	6 months/ 6 months (colch or naprox and lanso)[e]	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as an sUA ≥8.0 mg/dL on the Day -4 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[21]	The proportion of subjects whose sUA is <6.0 mg/dL at the Final Visit.	PEs, monitoring of AEs, clinical laboratory variables, concomitant medication use, vital signs, and 12-lead ECGs.
TMX-00-004	Fbx 40 mg QD, 80 mg QD, 120 mg QD; Pbo	Randomized, double-blind, parallel-group, placebo-controlled	153	4 weeks (option to continue in TMX-01-005)/ 2 weeks (colch)[f]	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as an sUA ≥8.0 mg/dL on the Day -2 Visit without a secondary cause; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[21]	The proportion of subjects whose sUA decreased to <6.0 mg/dL after treatment with study drug (Day 28).	PEs (w/fundoscopic eye exam), monitoring of AEs, clinical laboratory variables, concomitant medication use, vital signs, 12-lead ECGs, and xanthine/ hypo-xanthine assays.
C02-009	Fbx 80 mg QD, 120 mg QD, 240 mg QD; Allo 300/100 mg QD[c]; Pbo	Randomized, double-blind, parallel-group, active- and placebo-controlled	1072	28 weeks (option to continue in C02-021)/ 8 weeks (colch or naprox)[e]	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as an sUA ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[21]	The proportion of subjects whose last 3 sUA levels were <6.0 mg/dL.	PEs, monitoring of AEs, clinical laboratory variables, concomitant medication use, vital signs, and 12-lead ECGs.

AEs=adverse events; Allo=allopurinol; ARA = American Rheumatism Association; colch=colchicine; ECGs-electrocardiograms; Fbx=febuxostat; lanso=lansoprazole; naprox=naproxen; Pbo=placebo; PE=physical exam.

a Indicates the number of subjects who received at least 1 dose of study drug.
b Subjects with normal renal function and mild renal impairment randomized to allopurinol received 300 mg QD, and subjects with moderate renal impairment randomized to allopurinol received allopurinol 200 mg QD. Febuxostat doses were not adjusted based on renal function.
c Allopurinol 300 mg QD for subjects with serum creatinine ≤1.5 mg/dL at Day -2 or 100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at Day -2.
d Allopurinol 300 mg QD for subjects who had a serum creatinine ≤1.5 mg/dL at the study visit prior to the last visit of the previous study or 100 mg QD for subjects who had serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at the study visit prior to the last visit of the previous study.
e Prophylactic medications were colchicine 0.6 mg QD or naproxen 250 mg BID.
f Prophylactic medication was colchicine 0.6 mg BID.
g All subjects who received at least 1 dose of study drug were included in the safety analyses. Adjudicated cardiovascular events identified as Antiplatelet Trialists' Collaboration (APTC) (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) were summarized.

Study	Treatment Groups	Design	N[a]	Duration of Treatment/ Duration of Gout Flare Prophylaxis During Treatment	Study Population	Primary Efficacy Endpoint	Safety Assessments[g]
C02-010	Fbx 80 mg QD, 120 mg QD; Allo 300 mg QD	Randomized, double-blind, parallel-group, active-controlled	760	52 weeks (option to continue in C02-021)/ 8 weeks (colch or naprox)[e]	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as an sUA ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout. [11]	The proportion of subjects whose last 3 sUA levels were <6.0 mg/dL.	PEs, monitoring of AEs, clinical laboratory variables, concomitant medication use, vital signs, and 12-lead ECGs.
TMX-01-005	Fbx 40 mg QD, 80 mg QD, 120 mg QD	Open-label, safety extension	116	Up to 5.5 years/ 4 weeks (colch)[f]	Subjects who completed Study TMX-00-004.	The proportion of subjects whose sUA decreased to or was maintained at <6.0 mg/dL.	PEs (w/fundoscopic eye exam), monitoring of AEs, clinical laboratory variables, concomitant medication use, vital signs, 12-lead ECGs, and xanthine/ hypo-xanthine assays.
C02-021	Fbx 80 mg QD, 120 mg QD; Allo 300/100 mg QD[d]	Randomized, open-label, active-controlled, safety extension	1086	Up to 40 months/ 8 weeks (colch or naprox)[e]	Subjects who completed Studies C02-009 or C02-010.	The proportion of subjects whose sUA decreased to <6.0 mg/dL.	PEs, monitoring of AEs, clinical laboratory variables, concomitant medication use, vital signs, and 12-lead ECGs.

AEs=adverse events; Allo=allopurinol; ARA = American Rheumatism Association; colch=colchicine; ECGs-electrocardiograms; Fbx=febuxostat; lanso=lansoprazole; naprox=naproxen; Pbo=placebo; PE=physical exam.

a Indicates the number of subjects who received at least 1 dose of study drug.
b Subjects with normal renal function and mild renal impairment randomized to allopurinol received 300 mg QD, and subjects with moderate renal impairment randomized to allopurinol received allopurinol 200 mg QD. Febuxostat doses were not adjusted based on renal function.
c Allopurinol 300 mg QD for subjects with serum creatinine ≤1.5 mg/dL at Day -2 or 100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at Day -2.
d Allopurinol 300 mg QD for subjects who had a serum creatinine ≤1.5 mg/dL at the study visit prior to the last visit of the previous study or 100 mg QD for subjects who had serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at the study visit prior to the last visit of the previous study.
e Prophylactic medications were colchicine 0.6 mg QD or naproxen 250 mg BID.
f Prophylactic medication was colchicine 0.6 mg BID.
g All subjects who received at least 1 dose of study drug were included in the safety analyses. Adjudicated cardiovascular events identified as Antiplatelet Trialists' Collaboration (APTC) (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) were summarized.

Source: Clinical Overview, page 15 – 16

In the original submission dated 14 December 2004, the Applicant included reports of the two double-blind Phase 3 studies namely, Study #C02-009 and Study #C02-010, and the Phase 2 (Study #C TMX-00-004). The Applicant also submitted interim report of an open-label safety extension of Studies #C02-009 and #C02-010 under Study #C02-021, since at the time of the submission, this study was still ongoing. Statistical review of the efficacy results were conducted by Mohammad Atiar Rahman, Ph.D. Note that Dr. Rahman did not conduct a safety review of the drug.

Please refer to Dr. Rahman's review of the design, analysis plan, and efficacy results of Studies CTMX-00-004, C02-009 and C02-010 b(4)

The following is taken from Dr. Rahman's review (Conclusions and Recommendations Section).

> Since Study #C TMX-00-004 was an inadequately powered short term Phase 2 study and Study #C02-021 was an incomplete open label safety extension study, this reviewer's efficacy conclusion of the study drug was primarily based on Studies #C02-009 and #C02-010. However, results from the other two studies were also considered.
>
> The primary efficacy variable was the proportion of responders, defined as having the last three observed uric acid levels as less than 6.0 mg/dL. Since the length of Study #C02-009 was 28 weeks and that of Study #C02-010 was 52 weeks, for appropriate overall conclusion this reviewer considered data up to 28 weeks from each study. Based on the results from Studies #C02-009 and#C02-010 and also taking the outcomes of Studies #C TMX-00-004 and #C02-021 into account, this reviewer concludes that all doses of febuxostat showed statistically significant difference in efficacy compared to placebo. Results from both studies also demonstrated a superior efficacy of febuxostat 80 mg QD by a superiority margin of 13%, and by more than 13% for other doses.
>
> In this study the reduction of serum urate was considered as a surrogate to the reduction of gout flares. The treatment with all study doses of febuxostat showed highly statistically significant efficacy with respect to the reduction of serum urate. However, results from the secondary efficacy endpoints showed that the percentages of subjects requiring treatment for gout flare in febuxostat groups were not statistically significantly different from that of placebo or allopurinol group. The following table shows the percentages of subjects requiring treatment for gout flares in Studies #C 02-009 and #C 02-010, also percentage of subjects with incidence of gout flare in Study #TMX-00-004.

	Placebo	Febuxostat				Allopurinol
		40 mg	80 mg	120 mg	240 mg	
Study #C 02-009	55%		57%	62%	66%	51%
Study #C 02-010				64%	72%	65%
Study # TMX-00-004	37%	35%				

> Therefore, the strength of correlation of this surrogate variable to the reduction of gout flare can be questioned. A clinical judgment is required in this respect.

There was no new efficacy data submitted on 17 February 2006 (complete response to the first approvable letter).

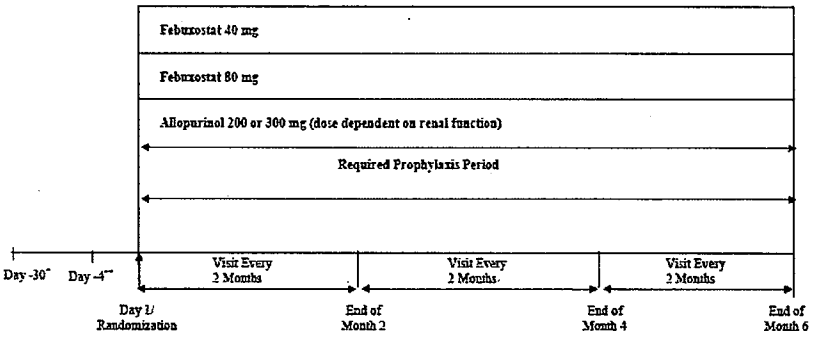
In this submission, the document provides results from the new, randomized, active-controlled, Phase 3 study (F-GT06-153) comparing the efficacy of febuxostat 40 mg and 80 mg QD to

allopurinol 300/200 mg QD (based on renal function) in reducing sUA level <6.0 mg/dL and incorporates new data from completed long-term extension studies TMX-01-005 and C02-021.

Study F-GT06-153 is a Phase 3, 6-month, randomized, double-blind, multicenter, active-controlled study designed to evaluate the efficacy and safety of febuxostat 40 mg once daily (QD) and 80 mg QD versus allopurinol in subjects with gout. The following is a summary of the study design (Figure 1):

> To qualify for randomization, subject must meet all admission criteria including sUA level was ≥8.0 mg/dL. Eligible subjects were randomized to 1 of 3 arms in a 1:1:1 ratio as follows: febuxostat 40 mg QD; or febuxostat 80 mg QD; or allopurinol. Randomization was stratified by baseline renal function and whether the subject finished either TAP Study TMX-01-005 or C02-021 in November/December 2006, upon completion of both studies.
>
> Subjects taking urate- lowering therapies (ULTs) discontinued them at the Screening Visit, and began taking colchicine 0.6 mg QD or, if not tolerated, naproxen 250 mg twice daily (BID) for gout flare prophylaxis with lansoprazole 15 mg QD for NSAID-associated ulcer prophylaxis for the duration of the study.
>
> Subjects randomized to allopurinol received either 300 mg QD or 200 mg QD, depending on renal function. Treatment duration was 6 months. Renal impairment was defined using estimated creatinine clearance (CL_{cr}) at baseline, where CL_{cr} was calculated using the Cockcroft-Gault formula corrected for Ideal Body Weight (IBW). Subjects with normal renal function (≥90 mL/min) and mild renal impairment (estimated CL_{cr} of 60 to 89 mL/min) randomized to allopurinol received 300 mg QD, and subjects with moderate renal impairment (estimated CL_{cr} 30 to 59 mL/min) randomized to allopurinol received 200 mg QD. No dose adjustment was done for subjects who were randomized to either one of the two febuxostat treatment groups. Of note, the enrollment criteria with regard to renal function varied across the randomized, controlled studies; however, the efficacy analyses were performed using renal function criteria which were consistent with the definitions applied in this study.

Figure 1: Study Design – F-GT06-153



* Day -30 Screening Visit was required for subjects who were taking ULTs. These subjects received TAP-provided prophylaxis medications on the Day -30 Screening Visit.
** Day -4 Visit was required for all subjects. It served as the Screening Visit for subjects who were not taking ULTs.

Source: Study Report, F-GT06-153, page 46

The completed long-term extension Study TMX-01-005 is a Phase 2, 5.5-year, open-label extension of Study TMX-00-004 and included doses of febuxostat 40 mg, 80 mg, and 120 mg QD. In addition, Study C02-021 is a Phase 3, randomized, up to 40-month, open-label, extension of Studies C02-009 and C02-010 and included doses of febuxostat 80 mg and 120 mg QD. This study also included an allopurinol comparator arm.

To make the efficacy section succinct, this review will focus on the results b(4)

In Study F-GT06-153, the primary endpoint is the proportion of subjects whose Final Visit serum urate (sUA) level was <6.0 mg/dL. This is in contrast to the two previous studies (Studies C02-009 and C02-010) in which the primary endpoint is defined as the proportion of subjects whose last three sUA levels were <6.0 mg/dL. According to the Applicant, the change in the primary efficacy endpoint for Study F-GT06-153 was reviewed and agreed upon by the FDA. I was not able to confirm this agreement/communication.

The analysis plan is described as follows:

> All sUA values collected from the start of the study to within 1 day, inclusive, of a subject's final dose were included in the primary efficacy analyses. Missing values were not imputed. However, if a subject prematurely discontinued from the study before the last sUA was obtained, then the subject's Final Visit would be the latest visit with an sUA occurring no later than 1 day postdosing. A subject's baseline value was used in the analysis if no postbaseline sUA was obtained.
>
> The primary comparison was febuxostat 40 mg QD versus allopurinol 300/200 mg QD. Secondary comparisons of febuxostat 80 mg QD versus allopurinol 300/200 mg QD and of febuxostat 40 mg QD versus febuxostat 80 mg QD were also performed.
>
> All primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population, which was defined as all randomized subjects who took at least 1 dose of study drug and who had baseline sUA ≥8.0 mg/dL. Unless otherwise specified, subjects receiving either allopurinol dose (200 mg or 300 mg) were analyzed together. All randomized subjects who took at least 1 dose of study drug were included in the safety analyses.
>
> The analysis of the primary efficacy variable for the primary comparison was performed sequentially using a closed testing procedure consisting of 2 steps.
>
> 1. In the first step, the 40-mg febuxostat treatment group was compared to the allopurinol treatment group to test for noninferiority. Binomial 95% confidence intervals, based on the normal approximation for the binomial distribution, were calculated for the difference between the febuxostat 40-mg and the allopurinol treatment groups. Noninferiority to allopurinol was to be declared if the value of the lower bound of the 95% confidence interval for the difference (ie, febuxostat 40 mg - allopurinol) was greater than -10%.
>
> 2. If febuxostat 40 mg was shown to be noninferior to allopurinol in step 1, then a test for superiority to allopurinol was to be performed. The test for superiority was to be performed using Fisher's exact test (two-tailed 0.05 significance level). The same Fisher's exact test would also be used to demonstrate substantial evidence of superiority based on the test being significant at the 0.001 level (two-tailed).
>
> Because of the closed testing procedure, no adjustments to the overall significance level were made. Secondary treatment comparisons were made comparing febuxostat 80 mg QD to

allopurinol 300/200 mg QD, and febuxostat 40 mg QD to febuxostat 80 mg QD using Fisher's exact test with two-tailed 0.05 significance level.

In all the Phase 3 studies, efficacy evaluations included sUA level measurement, physical assessment of tophi (except Study F-GT06-153), and gout flares.

3.1.2 DISPOSITION OF PATIENTS, DEMOGRAPHY AND BASELINE CHARACTERISTICS

Disposition of patients in Study TMX-00-004, Study C02-009 and Study C02-010 are described in Dr. Rahman's review. A summary of the disposition of patients in all Phase 3 randomized, controlled studies is presented in Appendix 1. In Study FGT06-153, a total of 2269 subjects were randomized into the study and took at least 1 dose of study drug. Of these, 757, 756, and 756 subjects were randomized and received febuxostat 40 mg QD, febuxostat 80 mg QD, and allopurinol, respectively. In the allopurinol group, 145 subjects received allopurinol 200 mg QD and 611 subjects received allopurinol 300 mg QD. One subject in the allopurinol group, whose baseline sUA was <8.0 mg/dL, was excluded from the ITT population.

Four hundred eighteen subjects (18%) prematurely discontinued the study. This is smaller compared to the discontinuation rate of Study C02-009 (28%) or Study C02-010 (33%). In study FGT06-153, 120 subjects (5%) dropped out within the first month on treatment. Like the two Phase 3 studies (C02-009 and C02-010), the most frequently reported primary reason for premature discontinuation was adverse events (AEs), followed by lost to follow-up. The percentages of subjects who prematurely discontinued due to an AE in the febuxostat 40-mg QD, febuxostat 80-mg QD, and allopurinol groups were 7%, 8%, and 9%, respectively. Only 12 subjects (1%) discontinued due to gout flare (7 in the febuxostat 80 mg QD group and 2 in the allopurinol group) compared to 28 subjects (9%) in Study C02-009 (13 in the febuxostat 80 mg QD group and 1 in the allopurinol group) and 47 subjects (19%) in Study C02-010 (10 in the febuxostat 80 mg QD group and 9 in the allopurinol group).

In Study FGT06-153, the mean number of days on study drug was 163 days. This is similar to Study C02-009 (approximately 161 days). The mean number of days on study drug was longer in Study C02-010 with approximately 284 days.

A summary of the demographic and baseline characteristics of patients in all the Phase 3 randomized, controlled studies is presented in Appendix 2. Most subjects were male (95%), the majority reported the use of alcohol (67%), and over one-half (63%) were obese (BMI ≥30 kg/m2). Approximately one-half of randomized subjects had a history of hypertension (49%), and approximately one-third had a history of hyperlipidemia (38%). In addition, 36% of subjects had a baseline sUA level of ≥10.0 mg/dL, and 21% had a history or presence of a tophus at baseline. According to the Applicant, due to differences in the enrollment criteria in Studies C02-009 and C02-010 compared to F-GT06-153, more subjects with renal impairment were included in study F-GT06-153 than in the other two pivotal Phase 3 studies. In Study F-GT06-153, 65% of ITT subjects (1483/2668) had mild to moderate renal impairment, which was defined as a baseline estimated creatinine clearance of 30 mL/min to 89 mL/min, inclusive. A total of 402 subjects (18%) had moderate renal impairment which was defined as a baseline estimated creatinine clearance of 30 mL/min to 59 mL/min, inclusive. Baseline characteristics of patients in Study TMX-00-004 are not that different from the Phase 3 studies.

3.1.3 PRIMARY EFFICACY ENDPOINT: PROPORTION OF PATIENTS WITH SERUM URIC ACID LEVELS < 6.0 mg/dL AT FINAL VISIT

As stated in Section 3.1.1, the primary endpoint in Study F-GT06-153 is the proportion of subjects whose Final Visit serum urate (sUA) level was <6.0 mg/dL. This is in contrast to the two previous studies (Studies C02-009 and C02-010) in which the primary endpoint is defined as the proportion of subjects whose last three sUA levels were <6.0 mg/dL. However, the results from the analysis of the primary endpoint defined as the proportion of subjects whose Final Visit serum urate (sUA) level was <6.0 mg/dL are reported in the label [redacted]

A statistical question is whether the results from Study C02-009 and Study C02-010 survived the multiplicity adjustment since this 'new' endpoint is just one of many secondary variables the Applicant looked at when they conducted the two Phase 3 studies. Another question is whether using the last observed value (i.e. LOCF) for the primary endpoint an appropriate approach to handle missing data due to patient dropout.

Of note, in the original primary efficacy analysis (i.e. test of superiority) for Studies C02-009 and C02-010, the Applicant applied a 'non-responder' status for subject who prematurely discontinued from the study before at least three serum urate levels were obtained. In the current submission, the Applicant used each subject's last visit score to identify subject's responder status (i.e. LOCF). Therefore, under this new approach, if a subject drops out of the study and his last visit's serum urate score is < 6.0 mg/dL, this subject is considered a "responder". Furthermore, only subjects with post-baseline measure are included in the analysis violating the 'intent-to-treat' principle.

b(4)

Table 2 summarizes the Applicant's results (symbol †) [redacted] and the result from my re-analyses of the data (symbol ‡) for the 'new' primary endpoint. In my analyses of the data, I applied a non-responder status to all patients who dropped of the study, as opposed to the Applicant's approach using the last observed value. Because the Applicant is requesting approval of febuxostat 40 mg and 80 mg QD, the results for doses 120 mg and 240 mg QD will not be reported.

When re-analyzing the primary efficacy data for Study FGT06-153, I found minor discrepancies with the Applicant's result using last observed value. However, the conclusions are similar; therefore, the results I generated are not reported.

In all Phase 3 studies (Applicant's results), the proportions of ITT subjects in the febuxostat 80 mg QD arm with Final Visit sUA levels <6.0 mg/dL were higher compared to the proportion of subjects in the allopurinol arm. Based on a test of superiority, the difference in the response rates of febuxostat 80 mg versus allopurinol is statistically significant.

Allopurinol is a commonly prescribed agent and is effective (compared to placebo) for managing hyperuricemia in patients with gout. In Study FGT06-153, a test of non-inferiority was applied to show febuxostat 40 mg QD is not worse than that of allopurinol on the basis of a minimally important clinical effect (i.e. a difference of -10%). The proportion of subjects in the febuxostat 40 mg with final visit sUA levels < 6.0 mg/dL was slightly higher compared to the proportion of subjects in the allopurinol. The difference in the proportions is 3% with the lower bound of the 95% confidence interval (-2%) greater than the pre-specified margin of -10%. This implies that febuxostat 40 mg QD is effective in reducing serum urate level in patients with gout.

Applying "non-responder" status to patients who discontinued treatment prior to end of the study and including all subjects randomized as denominator (as shown with symbol ‡) did not change the primary efficacy conclusions.

Table 2: Proportion of Subjects with Final Visit Serum Urate Levels < 6.0 mg/dL

Study	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Allopurinol	Placebo
C02-009				
N (ITT)		262	268	134
n/N_1(%) †		183/253 (72%)	102/263 (39%)	1/127 (1%)
95% CI*		33% (25%, 41%)		
p-value**		<0.0001		
n/N(%) ‡		126/262 (48%)	85/268 (32%)	1/134 (1%)
95% CI*		16% (8%, 24%)		
p-value**		<0.0001		
C02-010				
N (ITT)		255	250	
n/N_1(%) †		185/249 (74%)	88/242 (36%)	
95% CI*		38% (30%, 46%)		
p-value**		<0.0001		
n/N(%) ‡		133/255 (52%)	72/250 (29%)	
95% CI*		23% (15%, 31%)		
p-value**		<0.0001		
FGT06-153				
N (ITT)	757	756	755	
n/N_1(%) †	342/757 (45%)	507/756 (67%)	318/755 (42%)	
95% CI*	3% (-2%, 8%)	25% (20%, 30%)		
p-value**	0.233	<0.0001		
n/N(%) ‡	310/757 (41%)	452/756 (60%)	289/755 (38%)	
95% CI*	3% (-2%, 8%)	22% (17%, 26%)		
p-value**	0.288	<0.0001		
TMX-00-004	34	37		35
n/N(%)§	19/34 (56%)	28/37 (76%)		0/35 (0%)
p-value**	<0.0001	<0.0001		

† Source: Clinical Study report Study C02-009, Table 14.2.2.1 page 589, Study C02-010, Table 14.2.2.1 page 437, and Study FGT06-153 Table 14.2.1.2 page 526

‡ Reviewer's: In order for a subject to be considered a responder, the 'final' serum urate levels must have been <6.0 mg/dL. If a subject prematurely discontinued from the study before the 'final' serum urate level was obtained, the subject was considered a nonresponder. The denominator is all subjects randomized to treatment.

* 95% confidence interval comparing febuxostat versus allopurinol: $(p_1 - p_2) \pm 1.96 * se$

** p-value based on Fisher's exact test comparing febuxostat versus allopurinol

§ The primary endpoint is defined as the proportion of subjects whose serum urate level decreased to <6.0 mg.dL after treatment with study drug (Day 28).

Except for the primary efficacy comparison, that is, febuxostat 40 mg QD versus allopurinol 300/200 mg QD which was tested using a closed two-step testing procedure, no corrections for multiple comparisons were made in analyzing the other endpoints [redacted]. Either a multiplicity adjustment should have been applied in order to maintain an overall type 1 error rate, or the results should have been presented descriptively without p-values. Regardless, it is difficult to draw conclusions from the analyses of the secondary endpoints [redacted] from a statistical point of view because of the multitude of pairwise comparisons being tested and the clinical relevance of these endpoints. b(4)

3.1.4 Subgroup Analyses in Study FGT06-153

As a secondary analysis to the primary endpoint in Study FGT06-153, the Applicant evaluated a subgroup of subjects with mild-to-moderate renal impairment. According to the Applicant, the majority of subjects (65%) in this study had mild-to-moderate renal impairment (Table 3). This is defined as subject having baseline estimated creatinine clearance between 30 mL/min to 89 mL/min.

Table 3: Baseline Medical History (Study FGT06-153)

Variable	Treatment Group n (%)			
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)	All Subjects (N=2269)
History of Kidney Stone	104 (13.7)	121 (16.0)	104 (13.8)	329 (14.5)
Renal Function[a]				
Moderately Impaired[b]	130 (17.2)	136 (18.0)	136 (18.0)	402 (17.7)
Mildly Impaired	349 (46.1)	367 (48.5)	365 (48.3)	1081 (47.6)
Normal	278 (36.7)	253 (33.5)	255 (33.7)	786 (34.6)
Medical History of Diabetes	89 (11.8)	113 (14.9)	110 (14.6)	312 (13.8)
Medical History of Hypercholesterolemia	52 (6.9)	53 (7.0)	57 (7.5)	162 (7.1)
Medical History of Hyperlipidemia	299 (39.5)	308 (40.7)	335 (44.3)	942 (41.5)

a Moderately impaired: baseline ECC 30 mL/min to 59 mL/min; Mildly impaired: ECC 60 mL/min to 89 mL/min; Normal: ECC ≥90 mL/min.
b Includes 2 subjects with ECC <30 mL/min under the original protocol (Subjects 35371004 and 22995002).
Cross-reference: Statistical Table 14.1.8.1

Source: Study Report FGT06-153 Table 18, page 122

In the Clinical Studies Section of the Applicant's proposed label, it states

[redacted] b(4)

Table 4: Proportion of Mild-to-Moderate Renal Impairment Subjects with Final Visit Serum Urate Levels < 6.0 mg/dL – using last observed value

Study	Febuxostat 40 mg QD N=479	Febuxostat 80 mg QD N=503	Allopurinol N=501
n (%)	238 (50)	360 (72)	212 (42)
Difference (95%CI)*	7.4 (1.1, 13.6)	29.3 (23.4, 35.1)	
p-value	0.021	<0.001	

*difference in proportions between febuxostat and allopurinol; 95% confidence interval based on the normal approximation for the binomial distribution; p-value based on Fisher's exact test
Source: Clinical Overview 2008, Table 2.5.c, page 23

Like the primary endpoint, the last observed serum urate value is used to identify 'responder' regardless of patient dropout in the Applicant's results. The Applicant in the Study Report concludes that,

> Among the subjects with mild-to-moderate renal impairment, a statistically significantly higher proportion of subjects in the febuxostat 40-mg QD group had a final sUA of <6.0 mg/dL compared to allopurinol (p=0.021).
>
> In addition, the proportion of subjects with mild-to-moderate renal impairment who achieved an sUA level <6.0 mg/dL in the febuxostat 80-mg group was statistically significant higher compared to both the febuxostat 40-mg and allopurinol treatment groups (p<0.001 and p<0.001, respectively).

Considering that this is a secondary analysis to the primary endpoint, multiplicity may be an issue when interpreting the results. Therefore, the positive result when febuxostat 40 mg QD is compared to allopurinol is not that convincing.

The following table summarizes the result when "non-responder" status is applied to patients who discontinued treatment prior to end of the study. Numerically, a higher proportion of mild-to-moderate renal impairment subjects taking febuxostat 40 mg QD or 80 mg QD achieved a final visit serum urate levels less than 6.0 mg/dL compared to allopurinol. However, when non-responder status is applied to patients who discontinued, the difference in proportion is not statistically significant based on a test of superiority.

Table 5: Proportion of Mild-toModerate Renal Impairment Subjects with Final Visit Serum Urate Levels < 6.0 mg/dL – Re-analysis

	Febuxostat 40 mg QD N=479	Febuxostat 80 mg QD N=503	Allopurinol N=501
n (%)	214 (45%)	321 (64%)	198 (40%)
Diff (95% CI)	5% (-1%, 11%)	24% (18%, 30%)	
p-value	0.1024	<0.0001	

* 95% confidence interval comparing febuxostat versus allopurinol: $(p_1 - p_2) \pm 1.96 * se$ (difference in proportion based on normal approximation of binomial distribution

** p-value based on Fisher's exact test comparing febuxostat versus allopurinol

In general, there is insufficient evidence that febuxostat 40 mg QD is superior to allopurinol in this patient population (i.e. mild-to-moderate renal impaired patients). In contrast, there is evidence that febuxostat 80 mg QD is superior to allopurinol in this patient population.

According to the Applicant, eligible subjects were randomly assigned into one of the treatment groups.

> Randomization was stratified by baseline renal function and whether the subject finished either TAP Study TMX-01-005 or C02-021 in November/December 2006, upon completion of both studies.

Of the 2269 subjects enrolled in this study, 291 (13%) were previously enrolled in TMX-01005 or C02-021(Table 6). The number of subjects previously enrolled is well-balanced across treatment groups. The discontinuation rate is slightly lower in the febuxostat 40 mg QD compared to the other treatment groups.

Table 6: Patient Disposition by Previous Enrollment

	Febuxostat 40 mg QD N=757	Febuxostat 80 mg QD N=756	Allopurinol N=756
Completed (Total)	632 (83%)	598 (79%)	621 (82%)
Previously Enrolled	102 (13%)	91 (12%)	98 (13%)
Completed	98 (96%)	80 (88%)	90 (92%)
Discontinued	4 (4%)	11 (12%)	8 (8%)

When re-analyzing the primary efficacy data excluding subjects who were previously enrolled and applying the last serum urate level to identify responder, the conclusions are similar to that when all subjects are included in the analysis (Table 7). Applying the pre-specified non-inferiority margin, febuxostat 40 mg is determined to be non-inferior to allopurinol, with the lower bound of the 95% confidence interval of the difference (-3%) being greater than the pre-specified margin of -10%. The difference, however, in the response rate between the febuxostat 40-mg and allopurinol groups is not statistically significant. Based on a test of superiority, the difference in the response rates of febuxostat 80 mg versus allopurinol is statistically significant.

Table 7: Proportion of Subjects with Final Visit Serum Urate Levels < 6.0 mg/dL (Excluding Subjects in the long-term studies) – ITT Population

	Febuxostat 40 mg QD N=655	Febuxostat 80 mg QD N=665	Allopurinol N=657
n (%)	287(44%)	441 (66%)	272 (41%)
Diff (95% CI)	2.4% (-2.9, 7.8%)	25% (20%, 30%)	
p-value	0.3763	<0.0001	

* Result may slightly be different from the Applicant
95% confidence interval comparing febuxostat versus allopurinol: $(p_1 - p_2) \pm 1.96 * se$ (difference in proportion based on normal approximation of binomial distribution
p-value based on Fisher's exact test comparing febuxostat versus allopurinol

Reduction in Primary Tophus Size and Total Number of Tophi

The Applicant's approach to the analyses of the percent reduction in primary tophus size and the reduction in the total number of tophi is to perform an analysis on the subset of ITT subjects with a primary palpable tophus at baseline and with palpable tophi at baseline, respectively. The last tophus examination obtained prior to the first dose of study drug on Day 1 was used to determine a subject's inclusion in these populations, as well as the baseline primary tophus size and baseline total number of tophi.

In all studies, approximately 18 – 28% of subjects have tophus or palpable tophus at baseline. Because the analyses were done on a subgroup of patients (less than 30% of ITT population) and because of the numerous subgroup/secondary analyses performed to the primary endpoint, multiplicity may be an issue. Like the renal impairment subgroup, there is insufficient evidence that febuxostat 40 mg QD is superior to allopurinol in this patient population (i.e. mild-to-moderate renal impaired patients). In contrast, there is evidence that a higher proportion of subjects treated with febuxostat 80 mg QD achieved the serum urate level less than 6.0 mg /dL compared to allopurinol in this patient population. The result from the analysis of the subgroup is presented in Section 4.2.

Table 8: Subjects with Tophus and Palpable Tophus at Baseline

	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Allopurinol
Study C02-009		267	268
Presence of Tophus		64 (24%)	76 (28%)
Presence of Palpable Tophus		48 (18%)	64 (24%)
Study C02-010		256	253
Presence of Tophus		59 (23%)	62 (25%)
Presence of Palpable Tophus		52 (20%)	46 (18%)
Study FGT06153	757	756	756
Presence of Tophus	NA	NA	NA
Presence of Palpable Tophus	166 (22%)	163 (22%)	149 (20%)

Source: Clinical Study Report, Study C02-009, Table 11.2.c page 103; Study C02-010, Table 11.2.c, page 88; Study FGT06153, Table 14.1.7.1, page 281

3.1.5 SECONDARY ENDPOINTS

The following graphs present the proportion of subjects with serum urate level less than 6.0 mg/dL by visit, using the ITT population (i.e. all subjects randomized). I classified subjects who discontinued on or before the study visit as non-responders at that visit.

There is evidence that a higher proportion of subjects in febuxostat 80 mg QD have serum urate level less than 6.0 mg/dL as early as Visit 2 (or Week 2) in both Studies C02-009 and C02-010 compared to allopurinol. While the difference was maintained between febuxostat 80 mg QD and allopurinol, the proportion appears to plateau around Visit 28 (or Week 28) for febuxostat 80 mg Qd group, while the proportion of responders in the allopurinol group does not appear to change over time (stays roughly between 30 – 40%).

In Study FGT06-153, a higher proportion of subjects in febuxostat 80 mg QD have serum urate level less than 6.0 mg/dL as early as Month 2 compared to allopurinol (Figure 4). There appears to be no difference in the proportion of subjects with serum urate level less than 6.0 mg/dL between febuxostat 40 mg QD and allopurinol; the proportions of responders are smaller among subjects treated with febuxostat 40 mg QD or allopurinol compared to febuxostat 80 mg QD group.

Figure 2: Proportion of Subjects with Serum Urate Level < 6.0 mg by Visit - Study C02-009

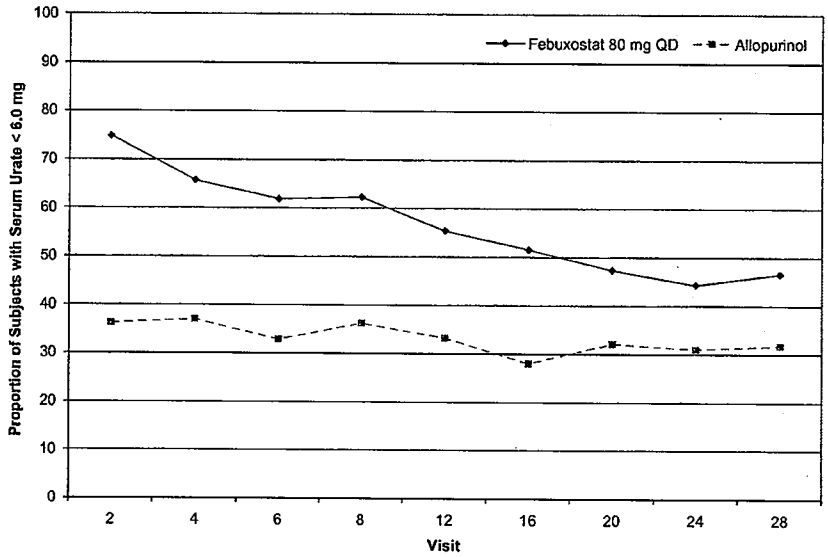


Figure 3: Proportion of Subjects with Serum Urate Level < 6.0 mg by Visit - Study C02-010

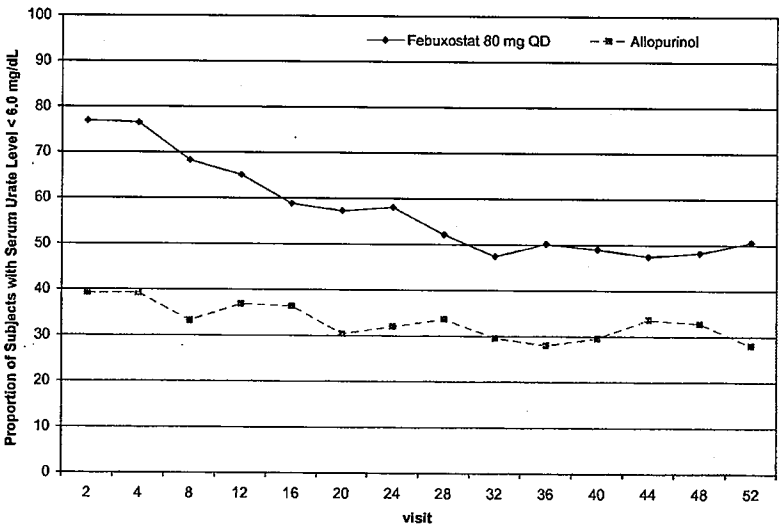
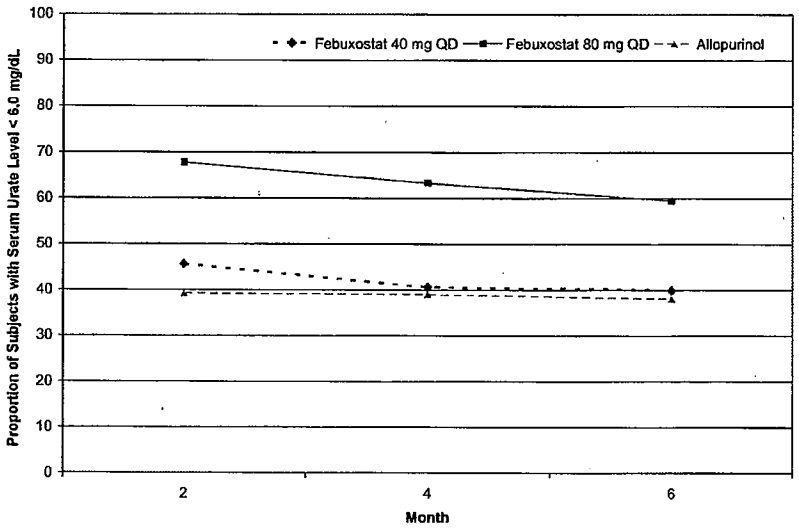


Figure 4: Proportion of Subjects with Serum Urate Level < 6.0 mg by Visit - Study FGT06153



Gout Flare

The applicant examined the reduction in incidence of gout flares by comparing the percentages of subjects who required treatment for flares.

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Gout flare is presented by calculating the number and percentage of subjects requiring treatment for gout flare over time. Subjects who discontinued were removed from the calculation; thus the calculation of percentage is based on data available for the interval of time being analyzed.

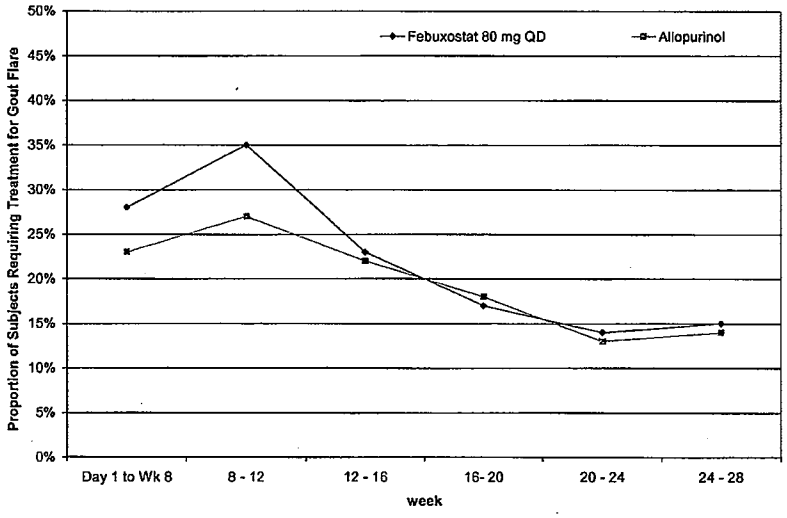
In Studies C02-009 and C02-010, prophylaxis is taken the first 8 weeks of treatment. In Study C02-009, the proportion of subjects requiring treatment for gout flare appears to be higher in the febuxostat 80 mg QD group compared to allopurinol (Table 9) during prophylaxis and during the entire 28 weeks. In Study C02-010, there appears to be no difference in the proportion of subjects requiring treatment for gout flare between febuxostat 80 mg QD and allopurinol (Table 10) at screening, during prophylaxis (Day 1 to Week 8), and during the entire 52 weeks.

In Study FGT06153, since all subjects are on prophylaxis the entire 6-month period, it is irrelevant to examine gout flares.

Although it is true that fewer subjects required additional treatment for gout flares when prophylaxis is used, it does appear that allopurinol-treated subjects require less treatment for gout flare compared to febuxostat. There is also a sharp increase in proportion requiring treatment when prophylaxis is discontinued; however, this proportion decreases over time in both treatment groups.

Only a slightly higher proportion of subjects prematurely discontinued due to gout flares at higher than recommended doses of ULORIC. In Studies C02-009 and C02-010, discontinuation rate is about 4% in the febuxostat 80 mg group, and about 6 – 7% in the febuxostat 120 mg or 240 mg groups. Of note, only 2% discontinued due to gout flares in the allopurinol group.

Figure 5: Proportion of Subjects Requiring Treatment for Gout Flare by Visit - Study C02-009



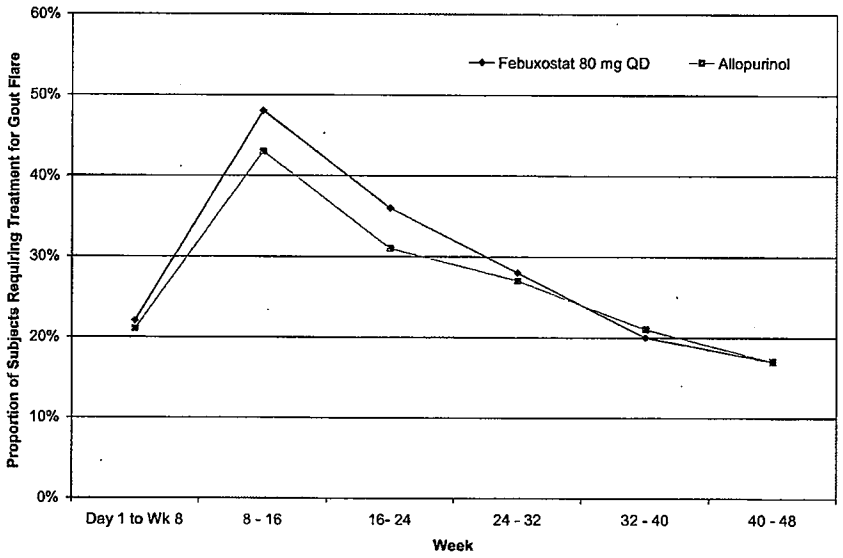
Source: Clinical Study Report, C02-009 Table 11.4m, page 142

Table 9: Proportion of Subjects Requiring Treatment for Gout Flare by Visit - Study C02-009

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
Time Interval	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Screening	12/134 (9%)	21/262 (8%)	28/269 (10%)	13/134 (10%)	20/268 (7%)
Day 1 to Week 28	74/134 (55%)	149/262 (57%)	168/269 (62%)[a]	89/134 (66%)[a]	136/268 (51%)
Day 1 to Week 8	27/134 (20%)	73/262 (28%)[a,b]	97/269 (36%)[a,b]	61/134 (46%)[a,b]	61/268 (23%)

Source: Clinical Study Report, C02-009 Table 11.4m, page 142

Figure 6: Proportion of Subjects Requiring Treatment for Gout Flare by Visit - Study C02-010



Source: Clinical Study Report, C02-010 Table 11.4m, page 108

Table 10: Proportion of Subjects Requiring Treatment for Gout Flare by Visit - Study C02-010

Time Interval	Febuxostat 80 mg QD n/N	(%)	Febuxostat 120 mg QD n/N	(%)	Allopurinol 300 mg QD n/N	(%)
Screening	20/255	(8%)	28/250	(11%)	20/251	(8%)
Day 1 to Week 52	163/255	(64%)	179/250	(72%)	163/251	(65%)
Day 1 to Week 8	55/255	(22%)[†]	90/250	(36%)[‡]	52/251	(21%)

Source: Clinical Study Report, C02-010 Table 11.4m, page 108

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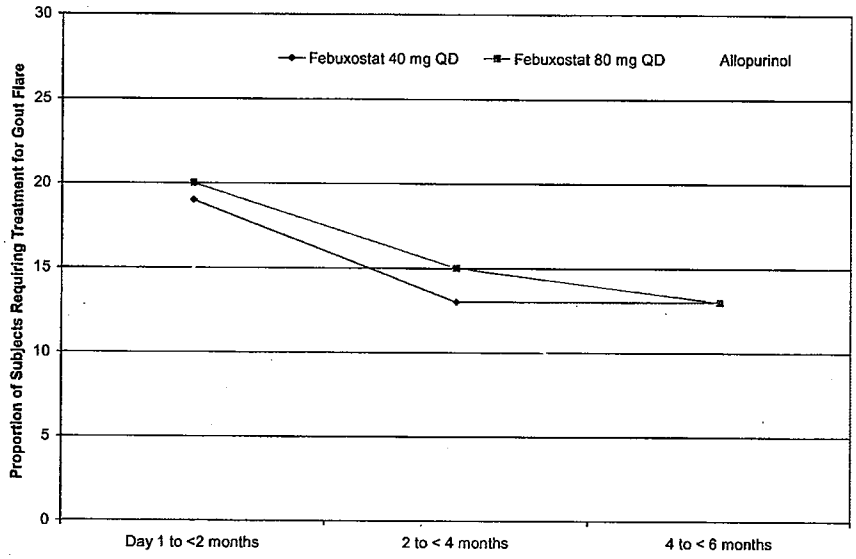
Figure 7: Proportion of Subjects Requiring Treatment for Gout Flare by Visit - Study FGT06153



Source: Clinical Study Report, FGT06153 Table 31, page 138

Table 11: Proportion of Subjects Requiring Treatment for Gout Flare by Visit - Study FGT06-153

Time Interval[a]	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=755)
	Subjects% (n/N)		
Washout/Screening [b]	5% (37/757)	7% (50/756)	5% (35/755)
Day 1 to Month 6	31% (237/757)*	31% (235/756)*	25% (186/755)
Day 1 to ≤2 Months	19% (146/757)*	20% (152/756)*	15% (115/755)
2 to ≤4 Months	13% (92/707)	15% (106/689)*	11% (76/689)
4 to ≤6 Months	13% (87/665)*	13% (81/635)*	8% (55/652)

a One month is the equivalent of 30 days. All gout flares with onset after Day 180 (including those reported ≤30 days since last dose) are summarized in the 4 to ≤6 Months interval. Gout flares with onset after last dose of study drug are summarized under the interval corresponding to last dose of study drug.
b The Washout/Screening time was different for each subject and ranged from 1 to 96 days.
* Indicates statistical significance versus allopurinol at p≤0.05.
Cross-reference: Statistical Table 14.2.3.1

Source: Clinical Study Report, FGT06153 Table 31, page 138

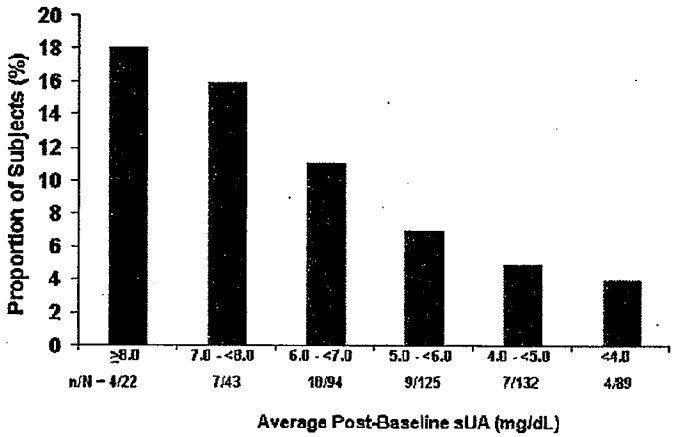
Long-term Reduction of Gout Flares

The Applicant examined the long-term reduction of gout flares in all Phase 3 studies and long-term extension studies. In Study C02-010, the Applicant examined the effect of serum urate reduction on the percentage of subjects requiring treatment for a gout flare. This is done by grouping subjects by their average postbaseline serum urate level regardless of treatment.

The following summarizes the result of the Applicant

> Subjects with lower average postbaseline sUA levels had fewer flares by the end of one year of treatment (Weeks 48 to 52) compared to subjects with higher average postbaseline sUA levels, and the frequency of gout flares decreased in direct proportion to postbaseline sUA level.

Figure 2.5.a. Proportion of Subjects Requiring Treatment for Gout Flare at the End of One Year of Treatment By Average Post-Baseline Serum Urate (Study C02-010)



Cross-reference: 2004 ISE, Statistical Table 3.2.2.26
Source: Clinical Overview 2008, page 25

This result is difficult to interpret because all febuxostat groups and allopurinol group are combined. Although there is evidence that febuxostat decreases the need to treat for gout flares, there is also evidence that allopurinol may work better than febuxostat in reducing gout flares. b(4)

Although one of the objectives of Study TMX-01-005 was to study long-term efficacy of febuxostat, analysis of gout flares is considered one of the additional efficacy endpoint that the Applicant examined. Furthermore, this study only has 116 subjects and there is no allopurinol arm. Thus, there is no assay sensitivity b(4)

b(4)

b(4)

Similarly, in Study C02-021, the primary objective was to study long-term safety. Although this study included subjects with up to 40 months of exposure and included allopurinol dose group, the analysis of gout flare is considered one of the secondary endpoints that the Applicant examined and no multiplicity adjustment was applied. Thus, similar concerns are being raised in this study

b(4)

b(4)

3.1.6 EFFICACY CONCLUSION

The updated label has several changes to the original label (from the first/second cycle submission of this NDA) in terms of efficacy. As stated in Section 3.1.1, there is a change in the definition of responder (i.e. primary endpoint) for Studies C02-009 and C02-010 from to just a single measurement (i.e. at Final Visit). Two statistical issues are noted because of this change. One is whether applying new definition to the primary endpoint and re-analyzing the data affects the Type 1 error and whether the Applicant's approach in handling missing data (i.e. last observed value) is appropriate on this endpoint. The results from the analyses of the primary endpoint in Studies C02-009 and C02-010 were highly significant ($p<0.0001$) such that applying multiplicity adjustment (e.g. Bonferroni) is not likely to change the overall conclusion. Furthermore, when applying a 'non-responder' status to patient who discontinued in all Phase 3 studies also did not alter the overall conclusion.

b(4)

gout flares. These are secondary endpoints the Applicant examined, and none of these were adjusted for multiplicity. There also problems in the interpretation of some of the results.

b(4)

In conclusion, the proportions of ITT subjects in the febuxostat 80 mg with Final Visit sUA levels <6.0 mg/dL were statistically significantly higher compared to the proportion of subjects in the allopurinol arm across all studies. In Studies C02-009 and C02-010, there is evidence that reduction in serum uric acid level to less than 6.0 mg per dL was noted in some patients by the Week 2 visit and was maintained throughout treatment (i.e. 28 weeks and 52 weeks, respectively). There is also evidence that febuxostat 80 mg QD is superior to allopurinol in patients with mild-to-moderate renal impairment.

In Study FGT06-153, there is some evidence that febuxostat 40 mg QD, although not superior, is effective in reducing serum urate level in patients with gout.

b(4)

3.2 EVALUATION OF SAFETY

As noted, this document currently submitted by the Applicant seeks to provide a complete response to each of the items identified by the Agency in the August 2, 2006 Approvable Letter for febuxostat NDA 21-856. In particular,

> Provide further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat in order to assure us that a dose level(s) with favorable risk-benefit characteristics has been defined.

On January 18, 2007, the Division met with the Applicant to discuss the efficacy and safety requirements for this product, and the following is one of the responses the Division gave to the Applicant regarding Safety:

> On its face, a study that demonstrates rates of APTC events for febuxostat 40 mg that are comparable to or lower than for allopurinol would be reassuring. However, if the study does not reproduce the possible cardiovascular safety signal seen in prior studies of febuxostat 80 and 120 mg then it would raise issues of assay sensitivity. However, provided that an adequate number of cardiovascular events are observed in the allopurinol control arm, if the rates of cardiovascular events in the febuxostat 40- and 80-mg arms are similar or lower than the rates in the allopurinol arm, then these results would still be both informative and potentially reassuring. A conclusion of safety for the febuxostat 40-mg dose will depend on a review of the totality of the data, including the risk of other cardiovascular events such as unstable angina, transient ischemic attacks, congestive heart failure and arrhythmias should also be carried out.

In this review, I will examine the results from the two original Phase 3 studies (C02-009 and C02-010) which were reviewed by Dr. Oussova during the second cycle, as well as the new Phase 3 study and the two completed long-term studies. For simplicity, the results will be based on the completed studies. As an example, the results from the two Phase 3 studies (C02-009 and C02-010) will be based on the second cycle submission dated February 17, 2006. The results for the two long-term studies and the new Phase 3 study will be based on this current submission. This review will focused on the following areas:

1. All-cause mortality
2. Cardiovascular mortality
3. Investigator-reported cardiovascular events
4. Adjudicated cardiovascular events

3.2.1 BACKGROUND

The following table (Table 12) summarizes the number of subjects in each of the Phase 2/3 randomized studies and the number of subjects who continued in the open-label long-term extension studies. This table also summarizes how these subjects were randomized in the open-label extension study. Table 13 summarizes the number of subjects in each of the long-term extension studies.

In Study TMX-004, 152 subjects were randomized and treated for four weeks. Of these, 116 (76%) subjects continued in the open-label extension study. All 116 subjects initially received 80 mg QD for four weeks in the open-label extension study. However, based on the serum urate levels, tolerance, or at the investigator's discretion, the febuxostat dose was titrated (up to 3 times between doses of 40, 80, or 120 mg) at study visits between Weeks 4 and 24. Subjects who failed to achieve a stable

dose at the end of 28 weeks were to be prematurely discontinued from the study. Of the 116 enrolled subjects in Study TMX-01005, 8 (7%), 79 (68%), and 29 (25%) subjects had final stable doses of febuxostat 40 mg QD, 80 mg QD, and 120 mg QD, respectively (Table 13).

In Study C02-009 and C02-010, 1832 subjects (1072 and 760, respectively) were randomized and treated for 28 weeks and 52 weeks, respectively. Of these, 1086 subjects (652 subjects from C02-009 and 434 subjects from C02-010) enrolled in the open-label extension study C02-021. In the original C02-021 protocol, subjects were assigned to receive febuxostat 80 mg QD. The dose could then be increased to 120 mg QD or subsequently decreased to 80 mg QD based on the subject's serum urate level, adverse events, or at the investigator's discretion. The protocol was amended in 2003 to introduce an allopurinol control group, with randomization to treatment. Therefore, of the 1086 subjects, 351 subjects enrolled before the amendment adding allopurinol arm and randomization scheme to treatment, and 735 subjects enrolled after the amendment. Subjects randomized to either febuxostat dose or to allopurinol could switch drug treatment based on serum urate level, AEs, or at the investigator's discretion. Of the 1086 subjects enrolled in Study C02-021, 606, 388, and 92 subjects had final stable treatment of febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD, respectively.

A total of 2269 subjects were enrolled in Study F-GT06-153 and received at least one dose of study drug. Of these, 757, 756, and 756 subjects were randomized and received febuxostat 40 mg QD, febuxostat 80 mg QD, or allopurinol, respectively. In the allopurinol group, 145 subjects received allopurinol 200 mg QD and 611 subjects received allopurinol 300 mg QD. Approximately 12% of subject in any treatment group had completed participation in Study C02-021 or TMX-01-005.

Table 12: Number of Subjects in the Phase 2/3 Controlled Studies

	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol	Placebo
Study TMX-04						
All treated	37	40	38			37
Went long-term?	28 (76%)	32 (80%)	27 (71%)			29 (78%)
Study TMX-01005		116				
Study C02-009						
All treated		267	269	134	268	134
Went long-term?		140 (52%)	172 (64%)	73 (54%)	182 (68%)	85 (63%)
Study C02-021		307	228		117	
Study C02-010						
All treated		256	251		253	
Went long-term?		143 (56%)	132 (53%)		159 (63%)	
Study C02-021		342	64		28	
Study FGT06-153						
All treated		757	756		756	

Table 13: Number of Subjects in the Long-Term Extension Studies

	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol
Study TMX-01005				
Phase 3				
Open-label: Initial		116		
Final	8	79	29	
Study C02-021				
Phase 3		649	292	145
Open-label: Initial		801	487	178
Final		606	388	92

Source: Clinical Study Report TMX-01005, page 90
Clinical Study Report C02-021, page 110, 176

The following table presents the extent of exposure in each of the Phase 3 studies and the long-term studies. In the Phase 2/3 randomized studies, the extent of exposure appears comparable across the febuxostat treatment groups. The extent of exposure in subjects treated with allopurinol appears longer compared to febuxostat treatment group. In contrast, in the long-term extension studies, the extent of exposure in subjects treated with allopurinol is shorter compared to febuxostat treatment group. Furthermore, exposure to febuxostat 80 mg QD is longer than febuxostat 120 mg QD. This could be attributed to the late addition of allopurinol arm in Study C02-021 and subjects are permitted to switch dose in the open-label extension studies. Of note, since subjects in the long-term extension studies may have switched dose more than once at any time interval, especially within the first 6 months of the study, the sum of the febuxostat 40-mg QD, 80-mg QD, and 120-mg QD dose columns may exceed 116 subjects in Study TMX-01005 and 1086 total subjects in Study C02-021.

Table 14: Summary of Exposure in Phase 2/3 Randomized-Controlled and Long-term Extension Studies

	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol	Placebo
Study TMX-004						
All treated	37	40	38			37
100/Person-Year	3	3	3			3
Mean (SD) Exposure, in days (d)	28 (1)	27 (4)	28 (4)			28 (4)
Study C02-009						
All treated		267	269	134	268	134
100/Person-Year		113	123	54	124	60
Mean (SD) Exposure, d		155 (66)	167 (60)	148 (72)	170 (60)	164 (64)
Study C02-010						
All treated		256	251		253	
100/Person-Year		201	182		211	
Mean (SD) Exposure, d		286 (126)	265 (138)		303 (117)	
Combined 009 and 010						
All treated		523	520	134	521	134
100/Person-Year		314	306	54	441	60
Mean (SD) Exposure, d		218 (120)	214 (115)	147 (72)	234 (114)	163 (64)
Study FGT06-153						
All treated		757	756		756	
100/Person-Year		344	332		338	
Mean (SD) Exposure, d		166 (47)	161 (52)		163 (50)	
Study TMX-005						
Initial Treatment	12	116	37			
100/Person-Year	38	272	76			
Mean (SD) Exposure, d	1146 (845)	857 (888)	752 (839)			
Final Stable Treatment	8	79	29			
Mean (SD) Exposure, d	1473 (820)	1201 (867)	864 (834)			
Study C02-021						
Initial Treatment		649	292		145	
100/Person-Year		1480	803		173	
Mean (SD) Exposure, d		692 (451)	601 (436)		363 (409)	
Final Stable Treatment		606	388		92	
Mean (SD) Exposure, d		854 (347)	719 (371)		596 (412)	

Study C02-009: Clinical Study Report Table 12.1a page 157
Study C02-010: Clinical Study Report Table 12.1a page 130
Combined: ISS-1 Table 2.3f page 80
Study TMX-005: Clinical Study Report Table 12.1a page 93, 135, 136
Study FGT06-153: Clinical Study Report Table 34 page 144
Study C02-021: Clinical Study Report Table 12.1a page 176
d=days

The following tables (Table 15, Table 17, Table 19 and Table 20) summarize the patient disposition in the Combined Phase 3 studies (Study C02-009 and C02-010), the new Phase 3 study (Study FGT06-153) and the two long-term extension studies. The timing of premature discontinuation for Studies C02-009 and C02-010 is summarized in Table 16, and for Study FGT06-153 in Table 18.

In the combined Phase 3 studies (Study C02-009 and Study C02-010), approximately 34% in the febuxostat arms and 24% in the allopurinol arm prematurely discontinued the study (Table 15). Of those who discontinued, only 7% were due to adverse events and 2% - 6% were due to gout flare. Thus, there were approximately 21% in the febuxostat arms and 15% in the allopurinol that discontinued for other reasons.

In Study C02-009, most of the discontinuation (~63%) occurred before Month 3 across all dose groups. Of the 300 subjects who prematurely discontinued, 96 subjects were due to gout flares or adverse events. Gout flares occurred as early as 20 days and as late as 140 days (mean 77 days) from the start of double-blind treatment, while adverse events occurred as early as Day 2 and as late as 174 days (mean 60 days) from the start of double-blind treatment. Meanwhile, of the 204 subjects (19%) who discontinued for other reasons, this occurred as early as 1 day and as late as 207 days (mean 72 days or around 2-½ months). This information is relevant since cardiovascular (CV) events were adjudicated post-hoc. Additional analyses regarding CV adverse events were also conducted post-hoc. Number of CV events may potentially be underestimated since ascertainment of CV events was done post-hoc and 19% (204 subjects) of the enrolled subjects discontinued due to reasons other than AE or gout flare prior to the end of the study.

In Study C02-010, 44% subjects discontinued before Month 3 and additional 27% discontinued between Month 3 and Month 6. Of the 252 subjects who prematurely discontinued, 94 subjects were due to gout flares or adverse events. Gout flares occurred as early as 7 days and as late as 305 days (mean 87 days) from the start of double-blind treatment, while adverse events occurred as early as Day 1 and as late as 322 days (mean 115 days) from the start of double-blind treatment. Meanwhile, of the 158 subjects (21%) who discontinued for other reasons, this occurred as early as Day 1 and as late as 336 days (mean 131 days or around 4-1/3 months). Like in Study C02-009, this information is relevant since cardiovascular events were adjudicated and additional analyses were performed post-hoc. Number of CV events may potentially be underestimated since ascertainment of CV events was done post-hoc and 15% (158 subjects) of the enrolled subjects discontinued due to reasons other than AE or gout flare prior to the end of the study.

Table 15: Reason for Premature Discontinuation – Studies C02-009 and C02-010

	Treatment Group n (%)					
		Febuxostat				Allopurinol
	Placebo (N=134)	All Doses (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)	240 mg QD (N=134)	300/100 mg QD (N=521)
Completed Study	101 (75%)	781 (66%)	342 (65%)	353 (68%)	86 (64%)	398 (76%)
Prematurely Discontinued	33 (25%)	396 (34%)	181 (35%)	167 (32%)	48 (36%)	123 (24%)
Primary Reason:						
Lost to follow-up	10 (7%)	88 (7%)	44 (8%)	35 (7%)	9 (7%)	38 (7%)
Adverse event	5 (4%)	84 (7%)	34 (7%)	39 (8%)	11 (8%)	26 (5%)
Personal reason(s)	9 (7%)	73 (6%)	35 (7%)	29 (6%)	9 (7%)	22 (4%)
Gout flare	0	65 (6%)	23 (4%)	34 (7%)	8 (6%)	10 (2%)
Other[a]	3 (2%)	54 (5%)	26 (5%)	22 (4%)	6 (4%)	19 (4%)
Protocol violation	3 (2%)	21 (2%)	13 (2%)	5 (<1%)	3 (2%)	7 (1%)
Therapeutic failure	3 (2%)	11 (<1%)	6 (1%)	3 (<1%)	2 (1%)	1 (<1%)

Phase 3 studies included: C02-009 and C02-010 combined data.

a "Other" reasons included: sponsor request, withdrew consent, noncompliance, doctor's decision due to concern with subject not being on allopurinol causing kidney stones, move out of state, need for prohibited medication, lack of efficacy, elevated liver function, sponsor's request, 24-hour Cl_{cr} below entry criteria, kidney donation, concern over persistently elevated blood pressure, administrative reasons, several gout flares, subject unblinded study drug, inability to discontinue exclusionary medication, and difficulty assessing disease under study due to concurrent diagnosis (osteoarthritis).

Cross-reference: Statistical Table 2.2.3 and Appendix 16.2-1.1 from Studies C02-009 and C02-010

Source: ISS-1 (Serial No. 0000), page 71

Table 16: Timing of Premature Discontinuation – Studies C02-009 and C02-010

Study C02-009	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD	All Subjects
All Randomized Subjects	134	267	269	134	268	1072
	n (%)					
Completed Study	101 (75%)	174 (65%)	200 (74%)	86 (64%)	211 (79%)	772 (72%)
Prematurely Discontinued	33 (25%)	93 (35%)	69 (26%)	48 (36%)	57 (21%)	300 (28%)
Timing of Premature Discontinuations (weeks)[a]						
<4	12 (36%)	20 (22%)	14 (20%)	15 (31%)	19 (33%)	80 (27%)
4 to <8	3 (9%)	18 (19%)	13 (19%)	13 (27%)	9 (16%)	56 (19%)
8 to <12	7 (21%)	16 (17%)	13 (19%)	5 (10%)	11 (19%)	52 (17%)
12 to <20	8 (24%)	25 (27%)	20 (29%)	10 (21%)	12 (21%)	75 (25%)
20 to <28	3 (9%)	14 (15%)	7 (10%)	5 (10%)	5 (9%)	34 (11%)
≥28	0	0	2 (3%)	0	1 (2%)	3 (1%)

Study C02-010	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD	All Subjects
All Randomized Subjects	256	251	253	760
	n (%)			
Completed Study	168 (66%)	153 (61%)	187 (74%)	508 (67%)
Prematurely Discontinued	88 (34%)	98 (39%)	66 (26%)	252 (33%)
Timing of Premature Discontinuations (weeks)[a]				
<4	15 (17%)	15 (15%)	12 (18%)	42 (17%)
4-<8	11 (13%)	20 (20%)	5 (8%)	36 (14%)
8-<12	10 (11%)	17 (17%)	6 (9%)	33 (13%)
12-<24	21 (24%)	25 (26%)	22 (33%)	68 (27%)
24-<36	17 (19%)	11 (11%)	12 (18%)	40 (16%)
36-<48	14 (16%)	10 (10%)	9 (14%)	33 (13%)
48-<52	0	0	0	0

Source: Clinical Study Report C02-009, Table 10.1A page 87
Clinical Study Report C02-010, Table 10.1A page 77

In Study FGT06-153, 66% subjects discontinued on or before Month 3 of study. Of the 418 subjects who prematurely discontinued, 186 (44%) subjects were due to gout flares or adverse events. Gout flares occurred as early as 4 days and as late as 169 days (mean 66 days) from the start of double-blind treatment, while adverse events occurred as early as Day 1 and as late as 179 days (mean 71 days) from the start of double-blind treatment. Meanwhile, of the 232 subjects (10%) who discontinued for other reasons, this occurred as early as Day 1 and as late as 231 days (mean 73 days or around 2-½ months). Number of CV events may potentially still be underestimated even though analyses of CV events were pre-specified since 10% (232 subjects) of the enrolled subjects discontinued due to reasons other than AE or gout flare prior to the end of the study and could potentially have CV events when followed.

Table 17: Reason for Premature Discontinuation – Study FGT06-153

Variable	Treatment Group n (%) Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)
Number of Subjects Prematurely Discontinued	125 (16.5)	158 (20.9)	135 (17.9)
Primary Reason for Premature Discontinuation			
Adverse Events	49 (6.5)	61 (8.1)	64 (8.5)
Protocol Violation	10 (1.3)	2 (0.3)	4 (0.5)
Personal reasons(s)	12 (1.6)	24 (3.2)	9 (1.2)
Lost to Follow-Up	28 (3.7)	33 (4.4)	28 (3.7)
Therapeutic Failure	1 (0.1)	1 (0.1)	1 (0.1)
Withdrew Consent	14 (1.8)	20 (2.6)	16 (2.1)
Did not Meet Inclusion/Exclusion Criteria	0	2 (0.3)	0
Gout Flare	3 (0.4)	7 (0.9)	2 (0.3)
Other	8 (1.1)	8 (1.1)	11 (1.5)
All Secondary Reasons for Premature Discontinuation[a]			
Protocol Violation	1 (0.1)	1 (0.1)	0
Personal reasons(s)	4 (0.5)	4 (0.5)	5 (0.7)
Lost to Follow-Up	3 (0.4)	1 (0.1)	1 (0.1)
Therapeutic Failure	2 (0.3)	1 (0.1)	0
Withdrew Consent	23 (3.0)	26 (3.4)	17 (2.2)
Gout Flare	4 (0.5)	4 (0.5)	0
Other	3 (0.4)	4 (0.5)	4 (0.5)

a Not all subjects had secondary reasons and some subjects may have had more than one secondary reason.
Cross-reference: Statistical Table 14.1.3

Source: Clinical Study Report FGT06-153 Table 9, page 104

Table 18: Timing of Premature Discontinuation – Study FGT06-153

Evaluation	Febuxostat 40 mg QD (N= 757)	Febuxostat 80 mg QD (N= 756)	Allopurinol 300/200 mg QD (N= 756)&	All Subjects (N= 2269)
Number of Subjects Randomized and Received At Least One Dose of Study Drug	757	756	756	2269
Number of Subjects Included in ITT Population ‡	757 (100.0%)	756 (100.0%)	755 (99.9%)	2268 (100.0%)
Reason for Exclusion from the ITT Population				
Serum Urate < 8.0 mg/dL at Day -4 Visit			1 (0.1%)	1 (0.0%)
Number of Subjects Prematurely Discontinued	125 (16.5%)	158 (20.9%)	135 (17.9%)	418 (18.4%)
Timing of Premature Discontinuation (days)				
1 to 30 [Month 1]	34 (4.5%)	48 (6.3%)	38 (5.0%)	120 (5.3%)
31 to 60 [Month 2]	16 (2.1%)	19 (2.5%)	28 (3.7%)	63 (2.8%)
61 to 90 [Month 3]	27 (3.6%)	37 (4.9%)	27 (3.6%)	91 (4.0%)
91 to 120 [Month 4]	15 (2.0%)	17 (2.2%)	10 (1.3%)	42 (1.9%)
121 to 150 [Month 5]	22 (2.9%)	20 (2.6%)	22 (2.9%)	64 (2.8%)
>= 151 [Month 6]	11 (1.5%)	17 (2.2%)	10 (1.3%)	38 (1.7%)

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
‡ The intent-to-treat population (ITT) is defined as all randomized subjects who received at least one dose of study drug and who had serum urate level >=8.0 mg/dL at the Day -4 Visit.

Source: Clinical Study Report FGT06-153 Table 14.1.2, page 260

In Study C02-021, approximately 39% subjects discontinued from the study and half of these subjects who discontinued occurred during the first year of the open-label extension. Of the 422 subjects who prematurely discontinued, 83 (20%) subjects were due to gout flares or adverse events.

Table 19: Reason for Premature Discontinuation – Study C02-021

Evaluation	Final Stable Treatment: Febuxostat 80 mg n (%)	Final Stable Treatment: Febuxostat 120 mg n (%)	Final Stable Treatment: Allopurinol 300 mg n (%)	All Subjects n (%)
Enrolled	606	388	92	1086
Prematurely Discontinued	194 (32.0)	171 (44.1)	57 (62.0)	422 (38.9)
Timing of Premature Discontinuation[a]				
Year 1	78 (12.9)	86 (22.2)	32 (34.8)	196 (18.0)
≤1 Month	11 (1.8)	9 (2.3)	3 (3.3)	23 (2.1)
1-2 Months	11 (1.8)	3 (0.8)	3 (3.3)	17 (1.6)
2-3 Months	5 (0.8)	7 (1.8)	3 (3.3)	15 (1.4)
3-6 Months	18 (3.0)	15 (3.9)	4 (4.3)	37 (3.4)
6-12 Months	33 (5.4)	52 (13.4)	19 (20.7)	104 (9.6)
Year 2	75 (12.4)	55 (14.2)	15 (16.3)	145 (13.4)
Year 3	41 (6.8)	30 (7.7)	10 (10.9)	81 (7.5)
Primary Reason for Premature Discontinuation				
Did Not Continue Under Amendment 4	1 (0.2)	1 (0.3)	2 (2.2)	4 (0.4)
Adverse Event	54 (8.9)	22 (5.7)	2 (2.2)	78 (7.2)
Protocol Violation	6 (1.0)	3 (0.8)	3 (3.3)	12 (1.1)
Personal Reason(s)	39 (6.4)	31 (8.0)	8 (8.7)	78 (7.2)
Lost to Follow-up[b]	42 (6.9)	39 (10.1)	9 (9.8)	90 (8.3)
Therapeutic Failure	10 (1.7)	38 (9.8)	22 (23.9)	70 (6.4)
Gout Flare	2 (0.3)	3 (0.8)	0	5 (0.5)
Other[c]	40 (6.6)	34 (8.8)	11 (12.0)	85 (7.8)

a The denominator is the number of subjects enrolled. A year is 365.25 days. A month is 30.44 days.
b Procedures for trying to contact subjects who were lost to follow-up included calling twice (documented in source documents) and sending a certified letter (proof of delivery kept on file). Attempts at contacting subjects were recorded as study notes when possible.
c Other reasons included: Site closure or other administrative issues (30 subjects), withdrawn consent (18 subjects), noncompliance (21 subjects), principal investigator or sponsor request (3 subjects), subject moving or traveling (3 subjects), subject chose not to continue with implementation of Amendment 3 or 4 (4 subjects), uncontrolled sUA (3 subjects), abnormal labs in C02-009, started another trial, started taking Celebrex, and chronic dietary indiscretions (1 subject each). One additional subject cited both moving and withdrawn consent as reasons for discontinuation, and one subject was discontinued both due to noncompliance and principal investigator request.

Cross-references: Statistical Table 14.1.2 and Appendices 16.2.1.1 and 16.2.8.5

Source: Clinical Study Report C02-021, page 110

In Study TMX01005, 50% subjects discontinued from the study and at least two-third of subjects who discontinued occurred during the first year of the open-label extension. Of the 58 subjects who prematurely discontinued, 21 (36%) subjects were due to gout flares or adverse events.

Table 20: Reason for Premature Discontinuation – Study TMX-01005

	Final Stable Dose[a]			
	Febuxostat 40 mg QD n (%)	Febuxostat 80 mg QD n (%)	Febuxostat 120 mg QD n (%)	All Subjects n (%)
Number of Subjects Enrolled	8	79	29	116
Number of Subjects Prematurely Discontinued	2 (25.0)	38 (48.1)	18 (62.1)	58 (50.0)
Timing of Premature Discontinuation				
Year 1	2 (25.0)	23 (29.1)	13 (44.8)	38 (32.8)
≤1 Month	0	7 (8.9)	0	7 (6.0)
1-2 Months	0	7 (8.9)	2 (6.9)	9 (7.8)
2-3 Months	0	1 (1.3)	2 (6.9)	3 (2.6)
3-6 Months	0	2 (2.5)	6 (20.7)	8 (6.9)
6-12 Months	2 (25.0)	6 (7.6)	3 (10.3)	11 (9.5)
Year 2	0	5 (6.3)	2 (6.9)	7 (6.0)
Year 3	0	4 (5.1)	1 (3.4)	5 (4.3)
Year 4	0	5 (6.3)	1 (3.4)	6 (5.2)
Year 5	0	1 (1.3)	0	1 (0.9)
Year 6	0	0	1 (3.4)	1 (0.9)
Primary Reason for Premature Discontinuation				
Personal Reason(s)	0	14 (17.7)	8 (27.6)	22 (19.0)
Adverse Event	1 (12.5)	10 (12.7)	2 (6.9)	13 (11.2)
Other[b]	1 (12.5)	6 (7.6)	2 (6.9)	9 (7.8)
Gout Flare	0	4 (5.1)	4 (13.8)	8 (6.9)
Lost to Follow-up	0	3 (3.8)	2 (6.9)	5 (4.3)
Protocol Violation	0	1 (1.3)	0	1 (0.9)

a Dose at the time of premature discontinuation.

b Other reasons for premature discontinuation include: unstable laboratory results, subject vacation, noncompliance, subject declined to continue participation, investigator discretion, sponsor request, uncontrolled sUA.

Cross-references: Statistical Table 14.1.2 and Appendix 16.2.1.1

Source: Clinical Study Report TMX-01005, page 90

In general, more than 50% of subjects remained in the trial as late as Year 3. As an example, at Year 1, there are approximately 82% in Study C02-021 and 67% in Study TMX-005 that are still in the trials. Approximately 69% in Study C02-021 and 61% in Study TMX-005 remained in the trial at Year 2, and approximately 61% in Study C02-021 and 57% in Study TMX-005 remained in the trial at Year 3.

3.2.2 ALL-CAUSE MORTALITY

In 2006, a total of 12 subjects died; all subjects who died were randomized to 1 of the febuxostat treatment groups. The death rate per 100 PY was 0.6 in the febuxostat groups and 0 in allopurinol group in phase 3 controlled studies; 0.4 for febuxostat versus 0 for allopurinol in long-term extension studies and 0.4 in the febuxostat group versus 0 in the allopurinol group in all studies combined.

In 2008 (this submission), 7 additional subjects died for a total of 19 deaths in the US program. Five of these deaths came from Study FGT06-153 (1 subject on febuxostat 40 mg QD, 1 subject on febuxostat 80 mg QD, and 3 subjects on allopurinol).and 2 additional subjects died in the long-term extension study (C02-021). The following are summaries of the results.

- In the combined Phase 3 RCT studies, a total of 9 subjects died. The death rate per 100 PY was 0.4 in the febuxostat groups and 0.5 in allopurinol group in phase 3 controlled studies. The unadjusted ratio is about 1.0 with 95% confidence interval from 0.2 to 4.0. There is no difference in result when adjusted for study. Events leading to death occurred between 56 to 287 days after subjects entered the study.

- In the long-term extension studies, a total of 10 subjects died. The death rate per 100 PY was 0.4 in the febuxostat groups and 0 in allopurinol group in phase 3 controlled studies. All of the deaths were reported in Study C02-021. There were no deaths in Study TMX-01-005. Events leading to death occurred between 203 to 1342 days after subjects entered the study. Six of the subjects who died were >65 years of age at baseline and 4 subjects were less than 65 years of age.

The Applicant considered these deaths to be unlikely or not related to study drug. There appears no discernible pattern with respect to treatment duration and time of death in the combined Phase 3 RCT studies and in the long-term extension studies.

Table 21: All-cause Mortality in Febuxostat Clinical Program by Patient-Year Exposure

Treatment	Patient-Years of Exposure	Number of Deaths	Rate Per 100 Patient-Years	95% Confidence Interval
Combined Phase 3 Randomized Controlled Studies (Studies C02-009 and C02-010)				
Febuxostat Total	671	4	0.6	0.16 - 1.52
Allopurinol 300/100 mg QD	334	0	0	0.00 - 1.11
Study FGT06-153				
Febuxostat Total	676	2	0.3	0.04 – 1.07
Allopurinol 300/200 mg QD	338	3	0.9	0.18 - 2.59
Combined all Phase 3 Studies				
Febuxostat Total	1347	6	0.4	0.16 – 0.97
Allopurinol 300/200 mg QD	672	3	0.5	0.09 – 1.30
Long-Term Extension Studies				
Febuxostat Total	2661	**10**	0.4	0.18 - 0.69
Allopurinol 300/100 mg QD	172	0	0	0.00 - 2.14

Source: Completeresponse-iss-1 Table 31, page 93
Updated-iss-iss-1, Table 3.3a page 70

3.2.3 CARDIOVASCULAR MORTALITY

In 2006, three CV deaths (0.3%) occurred during phase 3 controlled studies and seven CV deaths occurred in long-term extension studies with the overall rate of 0.3 per 100 PY. The incidence of deaths in the allopurinol group is 0.

In this submission, two CV deaths occurred in Study FGT06-153. Both deaths were in the allopurinol group. The total CV deaths during phase 3 controlled studies in the febuxostat group is three (0.1%) and two deaths (0.2%) in the allopurinol group. The unadjusted difference in proportion is -0.1% with 95% confidence interval of -0.4% to 0.3%. There is no difference in result when the model is adjusted for study.

Table 22: Cardiovascular Mortality in Febuxostat Clinical Program by Total Number of Subjects (N) or Patient-Year Exposure (PY)

Treatment	N	Number of CV Deaths	%	95% Confidence Interval
Combined Phase 3 Randomized Controlled Studies (Studies C02-009 and C02-010)				
Febuxostat 40 mg QD				-NA-
Febuxostat 80 mg QD	523	2	0.4	0.21 – 1.95
Febuxostat 120 mg QD	520	1	0.2	0.01 – 1.07
Febuxostat 240 mg QD	134	0	0	0 – 2.71
Febuxostat Total	*1177*	*3*	*0.3*	*0.05 – 0.74*
Allopurinol 300/100 mg QD	521	0	0	0 – 0.71
Study FGT06-153				
Febuxostat 40 mg QD	757	0	0	0 – 0.49
Febuxostat 80 mg QD	756	0	0	0 – 0.49
Febuxostat Total	*1513*	*0*	*0*	*0 – 0.24*
Allopurinol 300/200 mg QD	756	2	0.3	0.03 – 0.95
Combined all Phase 3 Studies				
Febuxostat 40 mg QD	757	0	0	0 – 0.49
Febuxostat 80 mg QD	1279	2	0.2	0.02 – 0.56
Febuxostat 120 mg QD	520	1	0.2	0.01 – 1.07
Febuxostat 240 mg QD	134	0	0	0 – 2.71
Febuxostat Total	*2690*	*3*	*0.1*	*0.02 – 0.33*
Allopurinol 300/200 mg QD	1277	2	0.2	0.02 – 0.57

Source: Completeresponse-iss-1 Table 51, page 161

Table 22 (continued)

Treatment	Patient Years	Number of CV Deaths	Rate Per 100 Patient-Years	95% Confidence Interval
Long-Term Extension Studies				
Febuxostat 40 mg QD	38	0	0	0 – 9.79
Febuxostat 80 mg QD	1746	4	0.2	0.06 – 0.59
Febuxostat 120 mg QD	878	3	0.3	0.07 – 1.00
Febuxostat Total	2661 PY	7	0.3	0.11 – 0.54
Allopurinol 300/100 mg QD	172 PY	0	0	0 - 2.14

Source: Completeresponse-iss-1 Table 55, page 182

3.2.4 EVALUATION OF CARDIOVASCULAR EVENTS

To address the Agency's concerns regarding the potential association of febuxostat and cardiovascular risk, additional analyses of cardiovascular events were performed by the Applicant in the second cycle and this current cycle based on:

- Blinded adjudication of cardiovascular events by cardiologists and neurologist using the criteria proposed by the APTC (Antiplatelet Trialists Collaboration) as later modified by Dr. White.
- Investigator-reported MedDRA terms meeting the primary and secondary APTC criteria as determined by TAP.

In the 2006 Safety Update (i.e. Second Cycle), the Applicant reported a total of 208 SAEs from 113 subjects and a total of 29 nonserious adverse events from 18 subjects. Of the 113 subjects with SAEs, 108 subjects were retrospectively identified in the database (Studies C02-009, C02-010, TMX-01-005, and C02-021). The remaining five were from other Phase 1 or 2 studies. All 18 subjects with nonSAEs were also retrospectively identified in the database (Studies C02-009, C02-010, TMX-01-005, and C02-021).

The consulting cardiovascular expert (Dr. William White from the University of Connecticut, School of Medicine in Farmington, Connecticut) was then provided with a blinded listing of all these events for review and adjudication of cardiac and neurologic events. Since the 2006 Safety Update, 28 additional subjects in Studies TMX-01-005 and C02-021 have been reviewed by the cardiovascular expert and adjudicated in a blinded fashion. Thus, a total of 136 subjects were adjudicated by the cardiovascular expert in Studies C02-009, C02-010, TMX-01-005, and C02-021.

The adjudicated diagnoses were placed into the following categories:

Category 1: APTC events
Category 2: Non-APTC cardiovascular thrombotic events
Category 3: CHF (including due to valvular disease)
Category 4: Arrhythmia, no evidence of ischemia
Category 5: Non-cardiovascular events

These categories were then analyzed in the following groups by treatment:

- APTC events only,
- APTC and non-APTC cardiovascular thrombotic events,
- All CV diagnoses including APTC events, non-APTC cardiovascular thrombotic events, congestive heart failure, non-ischemic arrhythmias,
- Non-ischemic arrhythmias.

Table 23 below summarizes the number of subjects with treatment-emergent CV adverse event, the number of subjects identified with serious CV AE and the number of subjects adjudicated, by treatment group and by study. As shown, none were adjudicated in Study TMX-04. Only one subject (in the febuxostat 80 mg QD) had treatment-emergent cardiovascular event. This subject's CV event was not considered serious and this subject was not adjudicated further.

Based on the analysis of the raw data, 18 subjects were adjudicated for APTC events in Study C02-009 and 26 subjects were adjudicated in Study C02-010. Of note, not all the subjects adjudicated have severe AEs, and not all subjects with severe CV AE were adjudicated. The distributions of subjects with treatment-emergent CV AE, with serious CV AE, and that were adjudicated were fairly balanced across treatment groups.

There were 88 subjects adjudicated for APTC events in Study C02-021. The proportion of subjects in this study with treatment-emergent CV, with serious CV AE, and that were adjudicated were lower in the allopurinol group compared to the febuxostat group. This could be attributed to the late addition of allopurinol arm and subjects are permitted to switch dose, as well as shorter length of exposure in the allopurinol arm.

There were 7 subjects adjudicated for APTC events in Study TMX-01005.

Table 23: Number (and percent) of Subjects with Treatment-emergent, Serious Cardiovascular Adverse Events, and Adjudicated Cardiovascular Events in Febuxostat Clinical Program

	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol	Placebo
Study TMX-04						
All treated	37	40	38			37
Treatment-emergent CV AE	0	1 (3)	0			0
Serious CV AE	0	0	0			0
# adjudicated	**0**	**0**	**0**			**0**
Study C02-009						
All treated		267	269	134	268	134
Treatment-emergent CV AE		15 (6)	15 (6)	8 (6)	12 (4)	4 (3)
Serious CV AE		6 (2)	5 (2)	1 (1)	2 (1)	1 (1)
# adjudicated		**7 (3)**	**6 (2)**	**2 (1)**	**2 (1)**	**1 (1)**
Study C02-010						
All treated		256	251		253	
Treatment-emergent CV AE		24 (9)	19 (8)		21 (8)	
Serious CV AE		7 (3)	8 (3)		9 (4)	
# adjudicated		**8 (3)**	**9 (4)**		**9 (4)**	
Study C02-021						
Initial Treatment		649	292		145	
Treatment-emergent CV AE		99 (15)	53 (18)		13 (9)	
Serious CV AE		47 (7)	21 (7)		7 (5)	
Adjudicated		**56 (9)**	**23 (8)**		**6 (4)**	
Study TMX-05						
Initial Treatment	12	116	37			
Treatment-emergent CV AE	2 (17)	16 (14)	6 (16)			
Serious CV AE	1 (8)	6 (5)	0			
Adjudicated		**7 (6)**				

Source: CompleteResponse-ISS-1, Table 45 page 131
CompleteResponse-ISS-1, Table 46 page 138

In Study FGT06-153, the blinded adjudication of cardiac and neurologic events was performed by an independent cardiovascular endpoints committee, which was comprised of 3 cardiovascular endpoints experts (2 cardiologists and 1 neurologist). The adjudication methodology, similar to the one performed by Dr. White for the Safety Update of 2006, was prospectively defined in the Charter for the Cardiovascular Endpoints Committee. All investigational sites were required to collect relevant clinical information necessary for adjudication of all deaths and potential cardiovascular events. Potential cardiovascular events included, but were not limited to, events such as syncope, loss of consciousness, chest pain, dyspnea, as well as myocardial infarction, stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolism, arrhythmia, and congestive heart failure. Of note, some of these conditions (e.g. elevated blood pressure, syncope, aortic aneurysms, vascular hypertensive disorders) were not used to classify potential CV events in the Safety Update of 2006.

The Cardiovascular Endpoints Committee determined if the reported events met the criteria for the APTC endpoints as specified below.

Adjudicated APTC events were categorized as follows:

- Cardiovascular Death
- Non-Fatal Myocardial Infarction
- Non-Fatal Stroke

Adjudicated non-APTC cardiovascular events were categorized as follows:

- Angina
- Coronary Revascularization
- Transient Ischemic Attack
- Cerebral Revascularization
- Venous and Peripheral Arterial Vascular Thrombotic Events
- Non-Fatal Congestive Heart Failure
- Arrhythmia, No Evidence of Ischemia
- Other Non-APTC CV Events (eg, severe hypertension)

A total of 205 subjects were adjudicated by the cardiovascular experts and they were well-distributed across treatment groups (Table 24). The distributions of subjects with treatment-emergent CV AE, and with serious CV AE were also fairly balanced across treatment groups.

Table 24: Treatment-emergent and Serious Cardiovascular Adverse Events and Number of Adjudicated Subjects in Study FGT06-153

	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Allopurinol
Study FGT06153			
All treated	757	756	756
Treatment-emergent CV AE	39 (5)	41 (5)	44 (6)
Serious CV AE	8 (1)	9 (1)	9 (1)
# adjudicated	**69 (9)**	**63 (8)**	**73 (10)**

Source: CompleteResponse-ISS-1, Table 44 page 127

3.2.4.1 Analysis of Investigator-Reported APTC Events

Investigator-reported MedDRA Preferred Terms for all adverse events in the clinical database that corresponded to the primary and secondary APTC events were identified by the Applicant. Primary APTC events were defined as follows: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and nonfatal cardiac arrest. Secondary APTC events included angina, coronary revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic events, and nonfatal congestive heart failure. Of note, nonfatal cardiac arrest and nonfatal congestive heart failure were not part of the APTC terms described in the literature, but were added by the Applicant as suggested by Dr. White and are included in the APTC event analyses in this document.

A list of APTC criteria and corresponding MedDRA Preferred Terms is presented in Table 25.

Table 25: APTC Criteria and Corresponding MedDRA Preferred Terms in the TAP Database for the Investigator-Reported Analyses

APTC Criterion	MedDRA Preferred Term	Category
Cardiovascular death	The following MedDRA Preferred Terms were associated with cardiovascular death: Acute Myocardial Infarction Cardiac Arrest Cardiac Failure Congestive Hypertensive Heart Disease Myocardial Infarction Retroperitoneal Haemorrhage Sudden Death	These events are summarized as primary APTC events in the analyses of investigator-reported APTC events.
Non-fatal myocardial infarction	Acute Myocardial Infarction Myocardial Infarction Silent Myocardial Infarction	
Non-fatal stroke	Brain Stem Infarction Cerebral Haemorrhage Cerebrovascular Accident Lacunar Infarction	
Non-fatal cardiac arrest	Cardiac Arrest	
Angina	Acute Coronary Syndrome Angina Pectoris Angina Unstable Myocardial Ischaemia	These events are summarized as secondary APTC events in the analyses of investigator-reported APTC events.
Revascularization	Arteriosclerosis Coronary Artery Coronary Artery Atherosclerosis Coronary Artery Disease Coronary Artery Occlusion Coronary Artery Stenosis	
Transient ischemic attack	Transient Ischaemic Attack	
Venous and peripheral arterial vascular thrombotic events	Deep Vein Thrombosis Embolism Ischaemia Pulmonary Embolism Thrombosis	
Non-fatal congestive heart failure	Cardiac Failure Congestive Cardiopulmonary Failure	

Cross-reference: Statistical Table 3.5

Source: Integrated Summary of Safety, page 37

Table 26 and Table 27 summarize investigator-reported primary APTC events and primary and/or secondary APTC events in the randomized controlled phase 3 trials. The results are broken down by study and by combined study.

The difference in proportion between febuxostat and allopurinol and the exact 95% confidence interval based on binomial distribution are calculated. The p-value is calculated using Fisher's exact test. Because the Applicant in this new submission reported risk ratio when comparing the treatment groups, the risk ratio between febuxostat and allopurinol and the 95% confidence interval for all relevant endpoints are calculated. This is done by dividing the rates between the two treatment groups. Continuity correction of 0.5 was used if either treatment group had zero events in calculating the risk ratio. The risk ratio when both studies are combined is also calculated with and without adjustment for study number. Test of homogeneity of the odds ratio is conducted using Breslow-Day method.

There are some caveats in reporting risk ratio. One may argue about the usefulness of the risk ratio and the relevance of the result to an individual patient or prescriber. Another is the potential misinterpretation of the risk involved. Note that risk ratio measures the strength of causal relationship. As an individual patient, it is more useful to know the excess risk of an adverse event with or without the study treatment (from risk difference) than the strength of the causal relationship between the treatments. Nonetheless, in this review, both are reported. In this review, the conclusions based on the 95% confidence intervals calculated, for both risk ratio and risk difference, are similar.

The overall rate of investigator-reported APTC events is higher in the febuxostat group compared with the allopurinol group in each study or when the studies are combined. In Studies C02-009 and C02-010, there were 9 events (0.8 %) among all febuxostat-treated patients, while there was only one event (0.2%) in the allopurinol group. The risk ratio between the two treatment groups is 4 (95% CI of 0.5, 32). The confidence interval includes the null value and values that correspond to a more favorable outcome with febuxostat than with allopurinol, so that the direction of the difference in risk, if any, is not known with much confidence. The same conclusion applies when each febuxostat dose is compared to allopurinol or when individual studies are examined.

Using the more inclusive criteria of investigator-reported primary and secondary APTC events, events were still observed more frequently in the febuxostat group than with allopurinol. However, like the primary APTC events, it is difficult to make any conclusion about the risk difference or ratio because of the wide confidence intervals and the uncertainty of the estimates.

The most common events in the febuxostat group were angina, revascularization and non-fatal MI. Except for revascularization, all events were seen at a higher rate with febuxostat compared with allopurinol and placebo (Appendix 3 to Appendix 4).

Table 26: Analysis of Subjects with Investigator-Reported APTC Events in Phase 3 Randomized Controlled Studies

Study	Event	Allopurinol	Febuxostat 80	Febuxostat 120	Total
C02-009	N	268	267	269	670*
	Primary (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	0	1 (0.4%) 0.4% (-0.7%, 1.5%) 3.0 (0.1, 75) 0.4991	1 (0.4%) 0.4% (-0.7%, 1.5%) 3.0 (0.1, 74) >0.999	2 (0.3%) 0.3% (-0.4%, 1.0%) 2.0 (0.1, 42) 0.3708
	Primary or Secondary Diff (95% CI)† Ratio (95%CI)‡ p-value*	1 (0.4%)	6 (2.3%) 1.9% (-0.4%, 4.2%) 6.1 (0.7, 51.3) 0.0683	3 (1.1%) 0.7% (-1.1%, 2.6%) 3.0 (0.3, 29.1) 0.6236	9 (1.3%) 1.0% (-0.4%, 2.4%) 3.6 (0.5, 28.9) 0.1900
C02-010	N	253	256	251	507
	Primary (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	1 (0.4%)	3 (1.2%) 0.8% (-1.1%, 2.7% 3.0 (0.3, 28.9) 0.6235	4 (1.6%) 1.2% (-0.9%, 3.3%) 4.1 (0.5, 36.8) 0.2150	7 (1.4%) 1.0% (-0.6%, 2.6%) 3.5 (0.4, 28.8) 0.2100
	Primary or Secondary Diff (95% CI)† Ratio (95%CI)‡ p-value*	6 (2.4%)	7 (2.7%) 0.4% (-2.8%, 3.5%) 1.2 (0.4, 3.5) >0.999	8 (3.2%) 0.8% (-2.5%, 4.1%) 1.4 (0.5, 4.0) 0.6010	15 (3.0%) 0.6% (-2.1%, 3.3%) 1.3 (0.5, 3.3) 0.6420
Combined	N	521	523	520	1177*
	Primary (%) Diff (95% CI)† Ratio (95%CI)‡ p-value* Adjusted Ratio§ p-value §	1 (0.2%)	4 (0.8%) 0.6% (-0.5%, 1.6%) 4.0 (0.4, 36.0) 0.3738 4.0 (0.5, 36) 0.5743	5 (1.0%) 0.8% (-0.3%, 1.9%) 5.0 (0.6, 43.4) 0.1237 5.1 (0.6, 44) 0.6273	9 (0.8%) 0.6% (-0.2%, 1.3%) 4.0 (0.5, 31.7) 0.1550 (0.5, 35) 0.6354
	Primary or Secondary Diff (95% CI)† Ratio (95%CI)‡ p-value* Adjusted Ratio§ p-value §	7 (1.3%)	13 (2.5%) 1.1% (-0.7%, 3.0%) 1.9 (0.7, 4.7) 0.2586 1.9 (0.7, 4.7) 0.1487	11 (2.1%) 0.8% (-1.0%, 2.6%) 1.6 (0.6, 4.1) 0.3548 1.6 (0.6, 4.2) 0.5271	25* (2.1%) 0.8% (-0.6%, 2.2%) 1.6 (0.7, 3.7) 0.2755 1.6 (0.7, 3.8) 0.3452

* In Study C02-009 and the combined, the total number of subjects includes subjects taking febuxostat 240 mg QD
† difference in proportion between treatment and allopurinol; exact confidence interval based on binomial distribution
‡ continuity correction of 0.5 was used if either treatment group had zero events
* p-value based on Fisher's exact test
§ Ratio adjusted by Study; p-value is based on Breaslow-Day test for Homogeneity of Odds Ratio

In Study FGT06153, there were 0, 1 and 3 subjects who experienced primary APTC events in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol 200/300 mg arms, respectively; this corresponds to an event rate of 0, 0.1 and 0.4%. For the combined febuxostat arms the event rate was 0.06%. Regarding secondary investigator-reported APTC events, the event rates were similar in the three study arms.

The most common events in the febuxostat group were angina, revascularization and non-fatal MI. Except for revascularization, all events were seen at a higher rate with febuxostat compared with allopurinol (Appendix 5).

Table 27: Analysis of Subjects with Investigator-Reported APTC Events in Study FGT06-153

Event	Allopurinol	Febuxostat 40	Febuxostat 80	Total Febuxostat
N	756	757	756	1513
Primary (%)	3 (0.4%)	0	1 (0.1%)	1 (0.1%)
Diff (95% CI)†		-0.4% (-0.2%, 1.0%)	-0.3% (-0.9%, 0.4%)	-0.3% (-0.9%, 0.2%)
Ratio (95%CI)‡		0.14 (0.0, 2.8)	0.3 (0.0, 3.2)	0.2 (0.0, 1.6)
p-value*		0.1245	0.6245	0.0768
Primary and Secondary	9 (1.2%)	7 (0.9%)	4 (0.5%)	11 (0.7%)
Diff (95% CI)†		-0.3% (-1.4%, 0.9%)	-0.7% (-1.7%, 0.4%)	-0.5% (-1.5%, 0.5%)
Ratio (95%CI)‡		0.8 (0.3,2.1)	0.4 (0.1, 1.4)	0.6 (0.3, 1.5)
p-value*		0.6271	0.2648	0.2657

† difference in proportion between treatment and allopurinol; exact confidence interval based on binomial distribution
‡ continuity correction of 0.5 was used if either treatment group had zero events
* p-value based on Fisher's exact test

Table 28 summarizes investigator-reported primary APTC events and primary/secondary APTC events in the long-term extension studies. Person-year is used as the denominator in calculating the rate. Unadjusted and adjusted (by study number) risk ratios and its exact confidence intervals are calculated and these are based on Poisson distribution.

The overall rate of investigator-reported primary APTC events is higher in the febuxostat group compared with the allopurinol group (1.2 versus 0.6 events/100 pt-years, respectively). All of the events in febuxostat 80 mg QD group occurred in Study C02-021. The unadjusted ratio between the febuxostat and allopurinol is 2.0 with 95% confidence interval of 0.3 to 15. The confidence interval includes the null value (i.e. 1.0) such that the direction of the difference in risk, if any, is not known with much confidence. The same conclusion applies when each febuxostat dose is compared to allopurinol.

Using the more inclusive criteria of investigator-reported primary and secondary APTC events, the proportion of subjects with events were comparable across different dose groups.

Table 28: Analysis of Subjects with Investigator-Reported APTC Events in Study C02-021 and the Combined Long-term Extension Studies in Patient-Year

Event	Allopurinol	Febuxostat 40	Febuxostat 80	Total Febuxostat*
Study C02-021				
PY	172		1480	2283
Primary (%) Ratio (95%CI)† p-value*	1 (0.6%)		21 (1.4%) 2.4 (0.3, 18) 0.3827	31 (1.4%) 2.3 (0.3, 17) 0.4031
Primary and Secondary Ratio (95% CI)† p-value*	6 (3.5%)		55 (3.7%) 1.1 (0.1, 1.4) 0.2648	83 (3.6%) 1.0 (0.5, 2.4) 0.9199
Long-Term Extension Studies				
PY (N)	172 (178)	38 (12)	1746 (917)	2661 (1143)
Primary (%) Ratio (95%CI)† p-value*	1 (0.6%)	1 (2.6%) 4.6 (0.3, 73) 0.2828	21 (1.2%) 2.1 (0.3, 15) 0.4767	31 (1.2%) 2.0 (0.3, 15) 0.4932
Primary and Secondary Ratio (95% CI)† p-value*	6 (3.5%)	1 (3%) 0.8 (0.1, 6.3) 0.8006	55 (3.1%) 0.9 (0.4, 2.1) 0.8145	83 (3.1%) 0.9 (0.4, 2.1) 0.7934

* The total number of subjects includes subjects taking febuxostat 120 mg QD
† Risk Ratio between treatment and allopurinol; exact confidence interval based on Poisson distribution
‡ Adjusted Risk Ration between treatment and allopurinol; exact confidence interval based on Poisson distribution (by Study)
* p-value based on Fisher's exact test

3.2.4.2 Analysis of Adjudicated APTC Events

The number and percentage of subjects who experienced cardiovascular events that were confirmed by adjudication to be APTC events are summarized overall in Table 29 and by APTC criterion for the Phase 3 RCT studies in Appendix 6 to Appendix 9 .

In Study C02-009, one subject (0.4%) in the febuxostat 80 mg QD group and one subject (0.4%) in the febuxotat 120 mg QD group experienced an adjudicated APTC event, while no subjects in the allopurinol group experienced an adjudicated APTC event. These events occurred 207 days and 64 days, respectively, from the start of the double-blind treatment. The difference in proportions between each febuxostat treatment group and allopurinol is 0.4% with confidence interval that includes the null value. The wide confidence intervals include values that correspond to a more favorable outcome with febuxostat than with allopurinol, so that the direction of the excess risk if any is not known with much confidence.

In Study C02-010, three subjects (1.2%) in the febuxostat 80 mg QD group, two subjects (0.8%) in the febuxotat 120 mg QD group, and one subject (0.4%) in allopurinol group experienced an adjudicated APTC event. These events occurred on average about 245 days from the start of the double-blind treatment in the febuxostat group and 341 days in the allopurinol group. The difference

in proportions between the total febuxostat and allopurinol is 0.6% with confidence interval that also includes the null value.

When these two studies are combined, a total of 7 subjects (0.6%) experienced an adjudicated APTC event in the febuxostat groups and one subject (0.2%) in the allopurinol group. The difference when the studies are combined is 0.4% and the unadjusted and adjusted risk ratio is about 3. Like the result from the individual studies, it is difficult to make any conclusion about the risk difference or ratio because of the wide confidence intervals and the uncertainty of the estimates.

In Study FGT06153, three subjects (0.4%) in the febuxostat 80 mg QD group and three subjects (0.4%) in allopurinol group experienced an adjudicated APTC event. No subject experienced adjudicated APTC event in the febuxostat 40 mg group. These events occurred on average about 169 days from the start of treatment in the febuxostat group and 119 days in the allopurinol group. There is no difference in proportion of adjudicated APTC event between febuxostat 80 mg group and the allopurinol group. Meanwhile, the wide confidence interval for the difference in proportion between febuxostat 40 mg and allopurinol suggests uncertainty on the direction of the excess risk.

When all three studies are combined, a total of 10 subjects (0.4%) experienced an adjudicated APTC event in the febuxostat groups and 4 subjects (0.3%) in the allopurinol group. The difference when the studies are combined is -0.1%, and the unadjusted and adjusted risk ratio is about 1.2. Like the result from the individual studies, it is difficult to make any conclusion about the risk difference or ratio because of the wide confidence intervals and the uncertainty of the estimates.

The number and percentage of subjects who experienced cardiovascular events that were confirmed by adjudication to be APTC events are summarized overall in Table 29 and by APTC criterion for the two long-term studies in Table 30.

A total of 27 subjects experienced an adjudicated APTC event in the febuxostat group (i.e. one subject taking febuxostat 40 mg, 17 subjects taking febuxostat 80 mg and 9 subjects taking febuxostat 120 mg). Only one subject in the allopurinol group experienced APTC event. Roughly, these events occurred around the first and second year after the start of the trial in the febuxostat group and about the third year in the allopurinol group. Although the rate of APTC events is higher with febuxostat than with allopurinol it is not possible to reach definitive conclusions about the risk because of the small number of events. Of note, the exposure to febuxostat was considerably greater than exposure to allopurinol, about 15 to 1, because most of the subjects in the open-label, long-term extension studies were treated with febuxostat.

Table 29: Analysis of Subjects with Adjudicated APTC Events

Study	Event	Allopurinol	Febuxostat 80	Febuxostat 120	Total
C02-009	**N**	**268**	**267**	**269**	**670**
	APTC (%)	0	1 (0.4%)	1 (0.4%)	2 (0.3%)
	Diff (95% CI)†		0.4% (-0.7%, 1.5%)	0.4% (-0.7%, 1.5%)	0.3% (-0.4%, 1.0%)
	Ratio (95%CI)‡		3.0 (0.1, 75)	3.0 (0.1, 74)	2.0 (0.1, 42)
	p-value*		0.4991	>0.999	0.3708
C02-010	**N**	**253**	**256**	**251**	**507**
	APTC (%)	1 (0.4%)	3 (1.2%)	2 (0.8%)	5 (1.0%)
	Diff (95% CI)†		0.8% (-1.1%, 2.7%)	0.4% (-1.3%, 2.1%)	0.6% (-0.9%, 2.0%)
	Ratio (95%CI)‡		3.0 (0.3, 28.9)	2.0 (0.2, 22.5)	2.5 (0.3, 21.6)
	p-value*		0.6235	0.6228	0.3860
C02-009 + C02-010	N	521	523	520	**1177**
	APTC (%)	1 (0.2%)	4 (0.8%)	3 (0.6%)	7 (0.6%)
	Diff (95% CI)†		0.6% (-0.5%, 1.6%)	0.4% (-0.6%, 1.3%)	0.4% (-0.3%, 1.1%)
	Ratio (95%CI)‡		4.0 (0.4, 36.0)	3.0 (0.3, 29.1)	3.1 (0.4, 25.4)
	p-value*		0.3738	0.3738	0.2638
	Adjusted Ratio§		4.0 (0.4, 36)	3.0 (0.3, 29)	3.4 (0.4, 28)
	p-value §		0.5743	0.5073	0.5771

Study	Event	Allopurinol	Febuxostat 40	Febuxostat 80	Febuxostat 120	Total
FGT06-153	N	756	757	756		1513
	APTC (%)	3 (0.4%)	0	3 (0.4%)		3 (0.2%)
	Diff (95% CI)†		-0.4% (-1.0%, 1.8%)	0.0 (-0.8%, 0.8%)		-0.2% (-0.8%, 0.4%)
	Ratio (95%CI)‡		0.14 (0.0, 2.8)	1.0 (0.2, 5.0)		0.5 (0.1, 2.5)
	p-value*		0.1245	>0.999		0.3855
Total	**N**	**1277**	757	**1279**	520	**2690**
	APTC (%)	**4 (0.3%)**	0	**7 (0.5%)**	3 (0.6%)	**10 (0.4%)**
	Diff (95% CI)†		-0.4% (-1.0%, 1.8%)	**0.2 (-0.4%, 0.8%)**	0.4% (-0.6%, 1.3%)	**-0.1% (-0.4%, 0.5%)**
	Ratio (95%CI)‡		0.14 (0.0, 2.8)	**1.8 (0.5, 6.0)**	3.0 (0.3, 29.1)	**1.2 (0.4, 3.8)**
	p-value*		0.1245	**0.3661**	0.3738	**0.7716**
	Adjusted Ratio§			**1.7 (0.5, 6)**		**1.2 (0.4, 3.9)**
	p-value §			**0.5291**		**0.3041**

* In Study C02-009 and the combined, the total number of subjects includes subjects taking febuxostat 240 mg QD
† difference in proportion between treatment and allopurinol; exact confidence interval based on binomial distribution
‡ continuity correction of 0.5 was used if either treatment group had zero events
* p-value based on Fisher's exact test
§ Ratio adjusted by Study; p-value is based on Breaslow-Day test for Homogeneity of Odds Ratio

Table 30: Analysis of Subjects with Adjudicated APTC Events – Long-term extension studies

Event	Allopurinol	Febuxostat 40	Febuxostat 80	Febuxostat 120	Total
PY	**172.2**	**37.7**	**1745.6**	**877.7**	**2660.9**
APTC (Rate per 100 PY) Ratio (95% CI)† p-value*	1 (0.6)	1 (2.7) 4.6 (0.3, 73) 0.2828	17 (1.0) 1.7 (0.2, 13) 0.6154	9 (1.0) 1.8 (0.2, 14) 0.5896	27 (1.0) 1.7 (0.2, 13) 0.5837
CV Death (Rate per 100 PY)	0	0	4 (0.2)	3 (0.3)	7 (0.3)
Nonfatal MI (Rate per 100 PY)	1 (0.6)	0	8 (0.5)	3 (0.3)	11 (0.4)
Nonfatal Stroke (Rate per 100 PY)	0	1 (2.7)	5 (0.3)	3(0.3)	9 (0.3)

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3.2.5 SAFETY CONCLUSION

In this submission, the Applicant collected information from a new study (Study FGT06153). This study includes 40 mg dose of febuxostat which addressed the Agency's recommendation to consider evaluating a lower dose of febuxostat. The study design specified collection of information on cardiovascular thromboembolic events and included a procedure for adjudication of potential APTC events by a blinded panel. The size of this new study is larger compared to the two previous Phase 3 studies combined (FGT06153: 2269 and Combined: 1698). The sample size was calculated based on efficacy and safety assumptions. The Applicant assumes an adjudicated APTC event rate of 0.6% for both febuxostat treatment groups and the allopurinol group. They stated that the sample size of 750 per treatment group would provide a 90% and 80% probability to expect that the observed relative risk of either febuxostat group to allopurinol is no greater than 2.344 and 1.750, respectively.

The Applicant also collected additional information from the completed long-term studies. The big question is whether the Applicant has adequately addressed the safety concern of febuxostat in terms of cardiovascular risk.

In the original and second cycle submissions, the Applicant tried to address the 'possible' imbalance in cardiovascular events by introducing the use of Antiplatelet Trialists' Collaboration (APTC) criteria in identifying cardiovascular events. The APTC criteria were applied to investigator-reported events and to events that were adjudicated by a cardiologist for Studies C02-009 and C02-010 and the then incomplete long-term studies (C02-021 and TMX01005).

Table 31 summarizes the results from safety analyses of the following areas:

1. All-cause mortality
2. Cardiovascular mortality
3. Investigator-reported cardiovascular events
4. Adjudicated cardiovascular events

In the data from 2006, there is evidence of potential imbalance of cardiovascular risk. In the Phase 3 randomized controlled trials (Studies C02-009 and C02-010), no deaths were observed in the allopurinol group, while four deaths were observed in the febuxostat arm. There was only one cardiovascular event in the allopurinol arm while seven were observed in the febuxostat arm. Although the risk difference is small (0.4%), the confidence interval is wide and includes the null value which reflects uncertainties in the estimated difference. We might say that the uncertainties are large compared to the estimated treatment effects. In the long-term studies, the results also did show some evidence of potential imbalance of cardiovascular risk. Like the short-term studies, the uncertainties are large compared to the estimated treatment effects.

One issue with the analyses of safety data from 2006 is that the application of APTC criteria and adjudication was introduced in a post hoc fashion. Thus, the analyses were performed post-hoc. The following are some of the potential issues that may result in differential estimates of CV risk.

1. In the short-term Phase 3 studies, there were at least 20% of subjects discontinued for reasons other than adverse events or gout flare. This information is relevant since these subjects may have CV events that were not captured because they were not in the study. According to the Applicant, these patients are only followed for 30 days after they discontinued.

2. Another reason to be cautious in interpreting the results from 2006 is the fact that some of the conditions (e.g. elevated blood pressure, syncope, aortic aneurysms, vascular hypertensive disorders) used to classify potential CV events in the current study (FGT-06153) were not used in the safety update of 2006. Furthermore, not all the subjects adjudicated have severe AEs, and not all subjects with severe CV AE were adjudicated.

One clinical issue is the small number of events. Patients with gout are expected to be older and have a greater risk for cardiovascular events. The fact that only small numbers of events were recorded produces some uncertainties about whether the findings definitely represented an increased risk of cardiovascular thromboembolic events with febuxostat.

Like the short-term Phase 3 trials, there are also problems with the long-term studies. In these studies, subjects were allowed to switch drug treatment based on serum urate level, AEs, or at the investigator's discretion over the entire length of treatment in Study C02-021 and between Weeks 4 to 24 in Study TMX-01005. The number of subjects and the extent of exposure in the allopurinol group are smaller (almost 15 to 1) compared to the febuxostat group. The studies were also not complete at the time of the safety update.

In the 2008 submission, new data from Study FGT06153 and from the long-term studies were collected. The results were slightly different from the previous trials. More deaths were observed in the allopurinol arm compared to the febuxostat arm. There were also more investigator-reported primary APCT events in the allopurinol arm compared to the febuxostat arm. Numerically, there is no difference in the number of adjudicated APTC event between febuxostat and allopurinol in this new study. When I combined all the information from all Phase 3 randomized controlled studies (Table 31), the differences between febuxostat and allopurinol are comparable suggesting no evidence in cardiovascular risk. The overall rate of mortality and cardiovascular mortality were comparable in both treatment groups, and so are the overall proportion of investigator-reported primary APTC and adjudicated APTC events. Although the observed difference in risk is small, the confidence intervals are wide suggesting uncertainties in the estimated treatment effect. Clearly, there could still be a possibility of an excess cardiovascular risk with febuxostat compared to allopurinol.

If we think of Studies C02-009 and C02-010 as an interim look, then the addition of information from Study FGT06-153 can be considered the second interim look. The question is whether this new study FGT06153 can be considered the final look in the study of cardiovascular events or do we need more data to understand the cardiovascular signal of febuxostat. If the objective of Study FGT06-153 was to confirm the cardiovascular safety signal of febuxostat, then this study did not satisfy that objective.

In the long-term studies, the overall rate of mortality and cardiovascular mortality, as well as the overall proportion of investigator-reported primary APTC and adjudicated APTC events were not increased from the 2006 to the 2008 submissions suggesting events occur early in the trial than later.

Based on the information collected, there are still uncertainties with regard to cardiovascular safety of febuxostat. Although the new study suggests no difference in risk between febuxostat and allopurinol, there is a lingering clinical question whether these studies produced sufficient number of events to adequately address cardiovascular risk. There is also a question with regards to the duration of exposure, particularly in the allopurinol arm.

Table 31: Summary of Safety Results

	2006				2008			
	Phase 3 RCT*		Long-Term**		Phase 3 RCT†		Long-Term**	
	Febuxostat	Allopurinol	Febuxostat	Allopurinol	Febuxostat	Allopurinol	Febuxostat	Allopurinol
All-Cause Mortality	4 0.6 per 100 PY	0	8 0.4 per 100 PY	0	6 0.4 per 100 PY	3 0.5 per 100 PY	10 0.4 per 100 PY	0
Cardiovascular Mortality	3 0.4 per 100 PY	0	6 0.3 per 100 PY	0	3 0.2 per 100 PY	2 0.3 per 100 PY	7 0.3 per 100 PY	0
Investigator-Reported APTC	9 0.8%	1 0.2%	29 1.5 per 100 PY	1 0.8 per 100 PY	10 0.4%	4 0.3%	31 1.2 per 100 PY	1 0.6 per 100 PY
Adjudicated APTC	7 0.6%	1 0.2%	21 1.1 per 100 PY	1 0.8 per 100 PY	10 0.4%	4 0.3%	27 1.0 per 100 PY	1 0.6 per 100 PY

* Includes Studies C02-009 and C02-010
** Includes Studies C02-021 and TMX-01005
† Includes Studies C02-009, C02-010 and FCT06153

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4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

4.1 SEX, RACE AND AGE

Subgroup analyses on the primary endpoint were conducted for the following baseline factors: age (<45, 45 to <65, ≥65), gender (male, female), race (black, other) in all three Phase 3 studies. The analyses were performed using a logistic regression model with treatment, baseline factor and the treatment by baseline factor interaction as fixed effects in the model.

According to the Applicant, none of the covariate adjusted analysis resulted in findings which differed from the primary analysis.

Table 33 summarizes the results from the subgroup analyses by demographic characteristics.

The male population comprised 95% of the subjects in each of the studies. There were no statistically significant treatment group-by-sex interactions observed in the proportion of subjects with serum urate less than 6.0 mg/dL, except in Study FGT06153. There appears to be a quantitive interaction between febuxostat 80 mg group and allopurinol. However, because of the small numbers of female subjects in the study sample, any claims in terms of subject's gender are essentially unsupported.

Similarly, the white population comprised approximately 70 – 75% of the subjects in each of the studies. There were no statistically significant treatment group-by-race interactions observed in the proportion of subjects with serum urate less than 6.0 mg/dL.

The Applicant stratified the age into three groups: < 45 years, 45 to 65, and ≥ 65 years; 84% of the population was younger than 65 years. Although no statistically significant treatment group-by-age interactions were observed in all three studies, as people aged, numerically higher proportion of subjects is responding to febuxostat. In Studies C02-009 and C02-010, there is also evidence that as people age, a numerically higher proportion of subjects respond to allopurinol.

Although it is true that because of the small numbers of patients greater than 65 years of age in the study sample, [redacted] his finding might be useful [redacted] b(4)

Table 32: Age in Years of Subjects with APTC Events

Study	Febuxostat 40	Febuxostat 80	Febuxostat 120	Allopurinol
C02-009 + C02-010		55, 65, 68	48, 60, 65, 77	62
FGT06-153		47, 59, 62		50, 66, 73
Long-term	66	Range: 46 – 75	Range: 41 – 84	77

Table 33: Proportion of Subjects with Final Visit Serum Urate Levels < 6.0 mg/dL by Demographic Characteristics using LOCF

	Study C02-009		Study C02-010		Study FGT06153		
	Febuxostat 80 mg QD N= 263	Allopurinol N=268	Febuxostat 80 mg QD N= 263	Allopurinol N=268	Febuxostat 40 mg QD N=757	Febuxostat 80 mg QD N=756	Allopurinol N=755
Total	183/253 (72%)	102/263 (39%)	185/249 (74%)	88/242 (36%)	342/757 (45%)	507/756 (67%)	318/755 (42%)
Age							
< 45	75	80	74	79	192	196	180
n (%)	45 (60%)	21 (26%)	43 (58%)	10 (13%)	67 (35%)	98 (50%)	56 (31%)
45 - 65	140	144	134	120	450	432	444
n (%)	104 (74%)	57 (40%)	102 (76%)	48 (40%)	208 (46%)	307 (71%)	200 (45%)
≥65	38	39	41	43	115	128	131
n (%)	34 (89%)	24 (62%)	40 (98%)	30 (70%)	71 (62%)	105 (82%)	63 (48%)
p-value (interaction)	0.9482		0.2192		0.2202	0.0837	
Female	16	19	12	8	35	46	47
n (%)	13 (81%)	9 (47%)	11 (92%)	6 (75%)	19 (54%)	39 (85%)	19 (40%)
Male	237	244	237	234	722	710	708
n (%)	170 (72%)	93 (38%)	174 (73%)	82 (35%)	327 (45%)	471 (66%)	300 (42%)
p-value (interaction)	0.8477		0.8028		0.3404	0.0282	
White	190	202	189	190	628	628	627
n (%)	140 (74%)	81 (40%)	146 (77%)	72 (38%)	297 (47%)	431 (69%)	273 (44%)
Others	63	61	60	52	129	128	128
n (%)	43 (68%)	21 (34%)	39 (65%)	16 (31%)	49 (38%)	79 (62%)	46 (36%)
p-value (interaction)	0.9617		0.5375		0.8219	0.9636	

** p-value using Logistic Regression comparing Febuxostat versus Allopurinol adjusting for treatment-by-covariate interaction.

4.2 OTHER SUBGROUPS AND SPECIAL POPULATIONS

Additional subgroup analyses on the primary endpoint were conducted for the following baseline factors: renal impairment (mild/moderate versus normal), baseline serum urate level (<10.0 versus ≥10.0 mg/dL), and the presence of tophi at baseline, in all three Phase 3 studies. The analyses were performed using a logistic regression model with treatment, baseline factor and the treatment by baseline factor interaction as fixed effects in the model. Some of the results for Study FGT06153 had been discussed in Section 3.1.4.

According to the Applicant, none of the covariate adjusted analysis resulted in findings which differed from the primary analysis.

In Studies C02-009 and C02-010, there were no statistically significant treatment group-by-renal impairment interactions, or treatment group-by-baseline tophi interactions, or treatment group-by-baseline serum urate interactions observed in the proportion of subjects with serum urate less than 6.0 mg/dL.

In Study FGT06-153, there were some qualitative interactions between renal impairment and treatment groups, as well as baseline serum urate level and treatment groups, when febuxostat 40 mg QD and allopurinol are being compared. A lower proportion of subjects taking febuxostat 40 mg QD that have no renal impairment at baseline, or that have baseline serum urate level of at least 10 mg/dL, achieved serum urate level of less than 6.0 mg/dL at the final visit, compared to allopurinol. In contrast, a higher proportion of subjects taking febuxostat 40 mg QD that have renal impairment at baseline, or that have baseline serum urate level of less than 10 mg/dL, achieved serum urate level of less than 6.0 mg/dL at the final visit, compared to allopurinol. However, because of the overall small difference in the proportion of subjects responding between febuxostat 40 mg QD and allopurinol, this qualitative interaction may not be as important.

In all three studies, a numerically higher proportion of subjects with renal impairment at baseline is responding better compared to subjects without renal impairment at baseline in both febuxostat and allopurinol groups. A numerically higher proportion of subjects without tophi at baseline is responding better compared to subjects with tophi at baseline in both febuxostat and allopurinol groups. A numerically higher proportion of subjects with baseline serum urate level of less than 10 mg/dL also responded better to either treatment compared to subjects with baseline serum urate level of at least 10 mg/dL. Like age, these findings might be useful

b(4)

Table 34: Proportion of Subjects with Final Visit Serum Urate Levels < 6.0 mg/dL by Baseline Characteristics using LOCF

	Study C02-009		Study C02-010		Study FGT06153		
	Febuxostat 80 mg QD N= 263	Allopurinol N=268	Febuxostat 80 mg QD N= 263	Allopurinol N=268	Febuxostat 40 mg QD N=757	Febuxostat 80 mg QD N=756	Allopurinol N=755
Total	183/253 (72%)	102/263 (39%)	185/249 (74%)	88/242 (36%)	342/757 (45%)	507/756 (67%)	318/755 (42%)
With Renal *	126	134	128	118	479	503	501
n (%)	98 (78%)	58 (43%)	98 (77%)	53 (45%)	239 (50%)	361 (72%)	213 (43%)
Without Renal	127	128	121	121	278	253	254
n (%)	85 (67%)	44 (34%)	87 (72%)	34 (28%)	107 (38%)	149 (59%)	106 (42%)
p-value (interaction)	0.6542		0.2185		0.0481	0.0160	
With Tophi *	59	73	58	59	166	163	148
n (%)	38 (64%)	26 (36%)	39 (67%)	20 (34%)	58 (35%)	94 (58%)	47 (32%)
Without Tophi	194	190	191	183	589	590	607
n (%)	145 (75%)	76 (40%)	146 (76%)	68 (37%)	287 (49%)	413 (70%)	272 (45%)
p-value (interaction)	0.4752		0.4873		0.9578	0.9446	
Baseline sUA ≥ 10	103	89	105	103	249	254	230
n (%)	62 (60%)	19 (21%)	71 (68%)	21 (20%)	66 (27%)	128 (50%)	71 (31%)
Baseline sUA < 10	150	174	144	139	508	502	525
n (%)	121 (81%)	83 (48%)	114 (79%)	67 (48%)	280 (55%)	382 (76%)	248 (47%)
p-value (interaction)	0.6357		0.0970		0.0257	0.0561	

** p-value using Logistic Regression comparing Febuxostat versus Allopurinol adjusting for treatment-by-covariate interaction.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The following are taken directly from Section 3.1.6 (Efficacy Conclusion) and Section 3.2.5 (Safety Conclusion).

The updated label has several changes to the original label (from the first/second cycle submission of this NDA) in terms of efficacy. As stated in Section 3.1.1, there is a change in the definition of responder (i.e. primary endpoint) for Studies C02-009 and C02-010 from [redacted] to just a single measurement (i.e. at Final Visit). Two statistical issues are noted because of this change. One is whether applying new definition to the primary endpoint and re-analyzing the data affects the Type 1 error and whether the Applicant's approach in handling missing data (i.e. last observed value) is appropriate on this endpoint. The results from the analyses of the primary endpoint in Studies C02-009 and C02-010 were highly significant ($p<0.0001$) such that applying a multiplicity adjustment (e.g. Bonferroni) is not likely to change the overall conclusion. Furthermore, applying a 'non-responder' status to patients who discontinued in all Phase 3 studies also did not alter the overall conclusion. b(4)

[redacted] gout flares. These are secondary endpoints the Applicant examined, and none of these were adjusted for multiplicity. There also problems in the interpretation of some of the results. b(4)

In conclusion, the proportions of ITT subjects in the febuxostat 80 mg with Final Visit sUA levels <6.0 mg/dL were statistically significantly higher compared to the proportion of subjects in the allopurinol arm. In Studies C02-009 and C02-010, there is evidence that reduction in serum uric acid level to less than 6.0 mg per dL was noted in some patients by the Week 2 visit and was maintained throughout treatment (i.e. 28 weeks and 52 weeks, respectively). There is also evidence that febuxostat 80 mg QD is superior to allopurinol in patients with mild-to-moderate renal impairment.

In conclusion, the proportions of ITT subjects in the febuxostat 80 mg group with Final Visit sUA levels <6.0 mg/dL were statistically significantly higher compared to the proportion of subjects in the allopurinol arm across all studies. In Studies C02-009 and C02-010, there is evidence that reduction in serum uric acid level to less than 6.0 mg per dL was noted in some patients by the Week 2 visit and was maintained throughout treatment (i.e. 28 weeks and 52 weeks, respectively). There is also evidence that febuxostat 80 mg QD is superior to allopurinol in patients with mild-to-moderate renal impairment.

In Study FGT06-153, there is some evidence that febuxostat 40 mg QD, although not superior, is effective in reducing serum urate level in patients with gout.

[redacted] b(4)

In terms of safety, the Applicant collected information from a new study (Study FGT06153). This study includes a 40 mg dose of febuxostat which addressed the Agency's recommendation to consider evaluating a lower dose of febuxostat. The study design specified collection of information on cardiovascular thromboembolic events and included a procedure for adjudication of potential

APTC events by a blinded panel. The size of this new study is larger compared to the two previous Phase 3 studies combined (FGT06153: 2269 and Combined: 1698). The sample size was calculated based on efficacy and safety assumptions. The Applicant assumes an adjudicated APTC event rate of 0.6% for both febuxostat treatment groups and the allopurinol group. They stated that the sample size of 750 per treatment group would provide a 90% and 80% probability to expect that the observed relative risk of either febuxostat group to allopurinol is no greater than 2.344 and 1.750, respectively.

The Applicant also collected additional information from the completed long-term studies. The big question is whether the Applicant has adequately addressed the safety concern of febuxostat in terms of cardiovascular risk which I am addressing below.

In the original and second cycle submissions, the Applicant tried to address the 'possible' imbalance in cardiovascular events by introducing the use of Antiplatelet Trialists' Collaboration (APTC) criteria in identifying cardiovascular events. The APTC criteria were applied to investigator-reported events and to events that were adjudicated by a cardiologist for Studies C02-009 and C02-010 and the then incomplete long-term studies (C02-021 and TMX01005).

In the data from 2006, there is evidence of potential imbalance of cardiovascular risk. In the Phase 3 randomized controlled trials (Studies C02-009 and C02-010), no deaths were observed in the allopurinol group, while four deaths were observed in the febuxostat arm. There was only one cardiovascular event in the allopurinol arm while seven were observed in the febuxostat arm. Although the risk difference is small (0.4%), the confidence interval is wide that includes the null value which reflects uncertainties in the estimated difference. We might say that the uncertainties are large compared to the estimated treatment effects. In the long-term studies, the results also did show some evidence of potential imbalance of cardiovascular risk. Like the short-term studies, the uncertainties are large compared to the estimated treatment effects.

One issue with the analyses of safety data in 2006 is that the application of APTC criteria and adjudication was introduced in a post hoc fashion. Thus, the analyses were performed post-hoc. The following are some of the potential issues that may result in differential estimates of CV risk.

1. In the short-term Phase 3 studies, there were at least 20% of subjects discontinued from reasons other than adverse events or gout flare. This information is relevant since these subjects may have CV events that were not captured because they were not in the study. According to the Applicant, these patients are only followed for 30 days after they discontinued.

2. Another reason to be cautious in interpreting the results from 2006 is the fact that some of the conditions (e.g. elevated blood pressure, syncope, aortic aneurysms, vascular hypertensive disorders) used to classify potential CV events in the current study (FGT-06153) were not used in the safety update of 2006. Furthermore, not all the subjects adjudicated have severe AEs, and not all subjects with severe CV AE were adjudicated.

One clinical issue is the small number of events. Patients with gout are expected to be older and have a greater risk for cardiovascular events. The fact that only small numbers of events were recorded produces some uncertainties about whether the findings definitely represented an increased risk of cardiovascular thromboembolic events with febuxostat.

Like the short-term Phase 3 trials, there are also problems with the long-term studies. In these studies, subjects were allowed to switch drug treatment based on serum urate level, AEs, or at the investigator's discretion over the entire length of treatment in Study C02-021 and between Weeks 4 to 24 in Study TMX-01005. The number of subjects and the extent of exposure in the allopurinol group are smaller (almost 15 to 1) compared to the febuxostat group. The studies are also not complete at the time of the safety update.

In the 2008 submission, new data from Study FGT06153 and from the long-term studies were collected. The results were slightly different from the previous trials. More deaths were observed in the allopurinol arm compared to the febuxostat arm. There were also more investigator-reported primary APCT events in the allopurinol arm compared to the febuxostat arm. Numerically, there is no difference in the number of adjudicated APTC event between febuxostat and allopurinol in this new study. When I combined all the information from all Phase 3 randomized controlled studies (Table 31), the differences between febuxostat and allopurinol are comparable suggesting no evidence in cardiovascular risk. The overall rate of mortality and cardiovascular mortality were comparable in both treatment groups, and so are the overall proportion of investigator-reported primary APTC and adjudicated APTC events. Although the observed difference in risk is small, the confidence intervals are wide suggesting uncertainties in the estimated treatment effect. Clearly, there could still be a possibility of an excess cardiovascular risk with febuxostat compared to allopurinol.

If we think of Studies C02-009 and C02-010 as an interim look, then the addition of information from Study FGT06-153 can be considered the second interim look. The question is whether this new study FGT06153 can be considered the final look in the study of cardiovascular events or do we need more data to understand the cardiovascular signal of febuxostat. If the objective of Study FGT06-153 was to confirm the cardiovascular safety signal of febuxostat, then this study did not satisfy that objective.

In the long-term studies, the overall rate of mortality and cardiovascular mortality, as well as the overall proportion of investigator-reported primary APTC and adjudicated APTC events were not increased from the 2006 to the 2008 submissions suggesting events occur early in the trial than later.

Based on the information collected, there are still uncertainties with regard to cardiovascular safety of febuxostat. Although the new study suggests no difference in risk between febuxostat and allopurinol, there is some lingering clinical question whether these studies produced sufficient number of events to adequately address cardiovascular risk. There is also some question with regards to the duration of exposure, particularly in the allopurinol arm.

5.2 CONCLUSIONS AND RECOMMENDATIONS

In view of the statistical findings generated from the analyses conducted by the Applicant and by me, I conclude that the proportions of ITT subjects in the febuxostat 80 mg with Final Visit sUA levels <6.0 mg/dL were statistically significantly higher compared to the proportion of subjects in the allopurinol arm across all studies. In Studies C02-009 and C02-010, there is evidence that reduction in serum uric acid level to less than 6.0 mg per dL was noted in some patients by the Week 2 visit and was maintained throughout treatment (i.e. 28 weeks and 52 weeks, respectively). There is also evidence that febuxostat 80 mg QD is superior to allopurinol in patients with mild-to-moderate renal impairment.

In Study FGT06-153, there is some evidence that febuxostat 40 mg QD, although not superior, is effective in reducing serum urate level in patients with gout.

b(4)

In terms of safety, based on the information collected thus far, there are still uncertainties with regard to cardiovascular safety of febuxostat. Although the new study suggests no difference in risk between febuxostat and allopurinol, there is some lingering clinical question whether these studies produced sufficient number of events to adequately address cardiovascular risk. There is also some question with regards to the duration of exposure, particularly in the allopurinol arm. Thus, I recommend that the Applicant conduct an outcome study as part of their Phase 4 commitment to adequately address the cardiovascular safety signal or other potential safety risk of febuxostat.

An advisory committee meeting was held last November 24, 2008 to discuss this application with the Arthritis Advisory Committee (AAC) members. The Division submitted four questions to the AAC for discussion. The questions include the safety of febuxostat, appropriate dosing, special population, and the committee's recommendation of whether to approve febuxostat for the treatment of chronic gout and what additional studies should be conducted post-approval to further assess the safety of the product. Although the advisory committee members expressed concerns about cardiovascular safety of febuxostat, they voted 12 to 0 (one abstention) to approve both the 40 mg QD and 80 mg QD doses of febuxostat. The committee members were convinced that there is a need for a new medication to treat gout, in part because some patients are intolerant of the current therapies (e.g. allopurinol) and in part because gout is treated suboptimally even when current therapies are appropriate. The advisory committee members also recommended that there should be an extensive post-marketing study to monitor safety. The design of the study was discussed (i.e. outcome study or observational study) but no consensus was reached.

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

7 APPENDIX

Appendix 1: Patient Disposition by Study

	Placebo	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol	Total
Study C-02-009							
Randomized Subjects	134		267	269	134	268	1072
Completed	101 (75%)		174 (65%)	200 (74%)	86 (64%)	211 (79%)	772 (72%)
Discontinued	33 (25%)		93 (35%)	69 (26%)	48 (36%)	57 (21%)	300 (28%)
Lost to follow-up	10 (30%)		19 (20%)	17 (25%)	9 (19%)	17 (30%)	72 (24%)
Adverse events	5 (15%)		18 (19%)	16 (23%)	11 (23%)	18 (32%)	68 (23%)
Personal reason(s)	9 (27%)		16 (17%)	16 (23%)	9 (19%)	9 (16%)	59 (20%)
Other	3 (9%)		15 (16%)	8 (12%)	6 (13%)	5 (9%)	37 (12%)
Gout flare	0		13 (14%)	6 (9%)	8 (17%)	1 (2%)	28 (9%)
Protocol Violations	3 (9%)		6 (6%)	3 (4%)	3 (6%)	6 (11%)	21 (7%)
Therapeutic failure	3 (9%)		6 (6%)	3 (4%)	2 (4%)	1 (2%)	15 (5%)
Study C-02-010							
Randomized Subjects			256	251		253	760
Completed			168 (66%)	153 (61%)		187 (74%)	508 (67%)
Discontinued			88 (34%)	98 (39%)		66 (26%)	252 (33%)
Lost to follow-up			25 (28%)	18 (18%)		21 (32%)	64 (25%)
Adverse events			16 (18%)	23 (23%)		8 (12%)	47 (19%)
Personal Reason(s)			19 (22%)	13 (13%)		13 (20%)	45 (18%)
Other			11 (13%)	14 (14%)		14 (21%)	39 (15%)
Gout flare			10 (11%)	28 (29%)		9 (14%)	47 (19%)
Protocol Violations			7 (8%)	2 (2%)		1 (2%)	10 (4%)
Study FGT06-153							
Randomized Subjects		757	756			756	2269
Completed		632 (83%)	598 (79%)			621 (82%)	1851 (82%)
Discontinued		125 (17%)	158 (21%)			135 (18%)	418 (18%)
Lost to follow-up		28 (4%)	33 (4%)			28 (4%)	89 (4%)
Adverse Events		49 (7%)	61 (8%)			64 (9%)	174 (8%)
Personal Reason(s)		12 (2%)	24 (3%)			9 (1%)	45 (2%)
Other		22 (3%)	30 (4%)			27 (4%)	79 (3%)
Gout flare		3 (0.4%)	7 (1%)			2 (0.3%)	12 (1%)
Protocol Violations		10 (1%)	2 (0.3%)			4 (0.5%)	16 (1%)
Therapeutic failure		1 (0.1%)	1 (0.1%)			1 (0.1%)	3 (0%)

Disposition of Patients in Study TMX-00-004

	Treatment Group			
	Placebo	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Febuxostat 120 mg QD
All Randomized Subjects	38	37	40	38
Completed Study	36	36	37	36
Prematurely Terminated	2	1	3	2
Primary Reason:				
Adverse Event	1	1	2	2
Gout Flare	1	0	0	0
Other	0	0	1[a]	0

a Subject non-compliant with study drug dosing.
Cross Reference: Statistical Table 14.1.2 and Appendix 16.2-1.1

Source: Clinical Study Report TXM-00-004, page 70

Appendix 2: Demographic and Baseline Characteristics – ITT Population

	Study C-02-009	Study C-02-100	Study FGT06-153	Total (Reviewer)	Total (Sponsor)†
ITT Population	1067	756	2268	4091	4091
Male	1000 (94%)	726 (96%)	2141 (94%)	3867 (95%)	3866 (95%)
Alcohol User	705 (66%)	500 (66%)	1549 (68%)	2754 (67%)	2753 (67%)
Mild to Moderate Renal Insufficiency [% with estimated Cl_{CR}<90mL/min]	538 (50%)	370 (49%)	1483 (65%)	2391 (58%)	2398 (59%)
History of Hypertension	501 (47%)	328 (43%)	1194 (53%)	2023 (49%)	2025 (49%)
History of Hyperlipidemia	348 (33%)	252 (33%)	942 (42%)	1542 (38%)	1542 (38%)
BMI ≥ 30	658 (62%)	469 (62%)	1442 (64%)	2569 (63%)	2568 (63%)
Mean BMI	32.7 kg/m²	32.5 kg/m²	32.8 kg/m²	32.7 kg/m²	32.7 kg/m²
Baseline sUA ≥ 10 mg/dL	416 (39%)	313 (41%)	733 (32%)	1462 (36%)	1462 (36%)
Mean baseline sUA	9.9 mg/dL	9.9 mg/dL	9.6 mg/dL	9.7 mg/dL	9.7 mg/dL
Experienced a gout flare in previous year	948 (89%)	660 (87%)	1875 (83%)	3483 (85%)	3482 (85%)

Source: Clinical Study Report C-02-009, pages 111 – 116; Clinical Study Report C-02-010 pages 93 – 98;
Clinical Study Report FGT06-153, pages 285 – 297;
†Summary of Clinical Efficacy pages 57 – 64

Demographic and Baseline Characteristics - Study TMX-00-004 (All Subjects)

	Study TMX-00-004
All Subjects	153
Male	136 (89%)
Alcohol User	-NA-
Mild to Moderate Renal Insufficiency [% with estimated Cl_{CR}<90mL/min]	-NA-
History of Hypertension	75 (49%)
History of Hyperlipidemia	71 (46%)
BMI ≥ 30	94 (61%)
Mean BMI	32.2 kg/m²
Baseline sUA ≥ 10 mg/dL	46 (33%) †
Mean baseline sUA	9.7 mg/dL
Experienced a gout flare in previous year	-NA-

Source: Clinical Study Report TXM-00-004, page 75 – 78
†ITT population

Appendix 3: Investigator-Reported Primary APTC – Studies C02-009 and C02-010

Table 3.6.e Incidence Rates and Confidence Intervals for Subjects with Investigator-Reported Treatment-Emergent Primary APTC Events in the Phase 3 Randomized Controlled Studies

	Treatment Group, n (%)					
	Placebo	Febuxostat				Allopurinol
Primary APTC Events	(N=134)	Total (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)	240 mg QD (N=134)	300/100 mg QD (N=521)
Overall	0	9 (0.8)	4 (0.8)	5 (1.0)	0	1 (0.2)
95% CI*	(0.00-2.71)	(0.35-1.45)	(0.21-1.95)	(0.31-2.23)	(0.00-2.71)	(0.005-1.07)
CV death	0	3 (0.3)	2 (0.4)	1 (0.2)	0	0
95% CI*	(0.00-2.71)	(0.053-0.74)	(0.046-1.37)	(0.005-1.07)	(0.00-2.71)	(0.00-0.706)
Non-fatal myocardial infarction	0	5 (0.4)	2 (0.4)	3 (0.6)	0	1 (0.2)
95% CI*	(0.00-2.71)	(0.14-0.99)	(0.046-1.37)	(0.119-1.68)	(0.00-2.71)	(0.005-1.065)
Non-fatal stroke	0	1 (0.08)	0	1 (0.2)	0	0
95% CI*	(0.00-2.71)	(0.002-0.47)	(0.00-0.70)	(0.005-1.07)	(0.00-2.71)	(0.00-0.706)
Non-fatal cardiac arrest	0	1 (0.08)	0	1 (0.2)	0	0
95% CI*	(0.00-2.71)	(0.002-0.47)	(0.00-0.70)	(0.005-1.07)	(0.00-2.71)	(0.00-0.706)

Studies included: C02-009 and C02-010
Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug.
a CI calculated based on binomial distribution
Cross-reference: Statistical Table 3.17.2.1

Source: Updated ISS-ISS-1 – SN033, page 120

Appendix 4: Investigator-Reported Primary or Secondary APTC – Studies C02-009 and C02-010

Table 3.6.f Incidence Rates and Confidence Intervals for Subjects with Treatment-Emergent Primary and Secondary Investigator-Reported APTC Events in the Phase 3 Randomized Controlled Studies

	Treatment Group, n (%)					
	Placebo	Febuxostat				Allopurinol
Primary and Secondary APTC Events	(N=134)	Total (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)	240 mg QD (N=134)	300/100 mg QD (N=521)
Overall	1 (0.7)	25 (2.1)	13 (2.5)	11 (2.1)	1 (0.7)	7 (1.3)
95% CI*	(0.019-4.09)	(1.38-3.12)	(1.33-4.31)	(1.06-3.75)	(0.019-4.09)	(0.54-2.75)
CV death	0	3 (0.3)	2 (0.4)	1 (0.2)	0	0
Non-fatal myocardial infarction	0	5 (0.4)	2 (0.4)	3 (0.6)	0	1 (0.2)
Non-fatal stroke	0	1 (<0.1)	0	1 (0.2)	0	0
Non-fatal cardiac arrest	0	1 (<0.1)	0	1 (0.2)	0	0
Angina	0	6 (0.5)	4 (0.8)	1 (0.2)	1 (0.7)	2 (0.4)
Revascularization	1 (0.7)	6 (0.5)	4 (0.8)	2 (0.4)	0	4 (0.8)
Transient Ischemic Attack	0	2 (0.2)	2 (0.4)	0	0	0
Venous and peripheral arterial vascular thrombotic events	0	2 (0.2)	0	2 (0.4)	0	0
Non-fatal congestive heart failure	0	3 (0.3)	2 (0.4)	1 (0.2)	0	1 (0.2)

Studies included: C02-009 and C02-010
a CI calculated based on binomial distribution
Cross-reference: Statistical Table 3.16.4.1 and 3.17.2.3

Source: Updated ISS-ISS-1 – SN033, page 122

Appendix 5: Investigator-Reported Primary or Secondary APTC – Study FGT06-153

Variable	Treatment Group n (%)		
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)
Total Subjects With at Least One Primary or Secondary Investigator-Reported APTC Event	7 (0.92)	4 (0.53)	9 (1.19)
Primary Investigator-Reported APTC Events			
Number of subjects with events	0	1	3
Rate (%)	0.00	0.13	0.40
95% Confidence Interval (%)[a]	(0.000, 0.486)	(0.003, 0.735)	(0.082, 1.155)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.125	0.625	
Versus Febuxostat 40 mg QD		0.500	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	0.14 (0.01, 2.76)	0.33 (0.03, 3.20)	
Versus Febuxostat 40 mg QD		3.00 (0.12, 73.63)	
Primary Investigator-Reported APTC Events by Criterion			
Cardiovascular death	0	0	2 (0.26)
Nonfatal myocardial infarction	0	1 (0.13)	1 (0.13)
Nonfatal stroke	0	0	0
Nonfatal cardiac arrest	0	0	0
Secondary Investigator-Reported APTC Events			
Number of subjects with events	7	3	6
Rate (%)	0.92	0.40	0.79
95% Confidence Interval (%)[a]	(0.373, 1.896)	(0.082, 1.155)	(0.292, 1.719)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	>0.999	0.507	
Versus Febuxostat 40 mg QD		0.343	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	1.17 (0.39, 3.45)	0.50 (0.13, 1.99)	
Versus Febuxostat 40 mg QD		0.43 (0.11, 1.65)	
Secondary Investigator-Reported APTC Events by Criterion			
Angina	2 (0.26)	1 (0.13)	0
Coronary revascularization	2 (0.26)	0	3 (0.40)
Transient ischemic attack	1 (0.13)	1 (0.13)	1 (0.13)
Venous or arterial vascular thrombotic events	0	1 (0.13)	1 (0.13)
Nonfatal congestive heart failure	3 (0.40)	0	2 (0.26)

N = number of subjects dosed; QD = once daily.
a Exact confidence interval based on Binomial Distribution.
b Continuity correction of 0.5 was used if either treatment group had zero APTC events.
Cross-references: Statistical Tables 14.3.1.15 and 14.3.1.16.1

Source: Clinical Study Report, FGT06153, Table 41 page 159

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Appendix 6: Analysis of Adjudicated APTC - Study C02-009

Event	Allopurinol	Febuxostat 80	Febuxostat 120	Total
N	**268**	**267**	**269**	**670**
APTC (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	0	1 (0.4%) 0.4% (-0.7%, 1.5%) 3.0 (0.1, 75) 0.4991	1 (0.4%) 0.4% (-0.4%, 1.1%) 3.0 (0.1, 74) >0.999	2 (0.3%) 0.3% (-0.4%, 1.0%) 2.0 (0.1, 42) 0.3708
CV Thromboembolic Event (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	0	4 (1.5%) 1.5% (-0.3%, 3.3%) 9.2 (0.5, 171) 0.0613	2 (0.7%) 0.7% (-0.3%, 1.8%0 5.0 (0.2, 105) 0.4991	6 (0.9%) 0.9% (-0.1%, 1.9%) 5.3 (0.3, 94) 0.1203
All CV events Diff (95% CI)† Ratio (95%CI)‡ p-value*	1 (0.4%)	5 (1.9%) 1.5% (-0.7%, 3.7% 5.1 (0.6, 43.9) 0.1225	4 (1.5%) 1.1% (-0.5%, 2.7%) 4.0 (0.4, 36.3) 0.3727	10 (1.5%) 1.1% (-0.3%, 2.6%) 4.0 (0.5, 32) 0.1505
Non-ischemic Event Diff (95% CI)† Ratio (95%CI)‡ p-value*	1 (0.4%)	1 (0.4%) 0.0 (-1.4%, 1.4%) 1.0 (0.1, 16.1) >0.999	1 (0.4%) -0.0 (-1.0%, 1.0%) 1.0 (0.1, 16) >0.999	3 (0.4%) 0.1% (-1.0%, 1.2%) 1.2 (0.1, 11.6) 0.8742
Non CV Event Diff (95% CI)† Ratio (95%CI)‡ p-value*	1 (0.4%)	2 (0.8%) 0.4% (-1.2%, 2.0%) 2.0 (0.2, 22.4) 0.6236	1 (0.4%) 0.0 (-1.0%, 1.0%) 1.0 (0.1, 16) >0.999	4 (0.6%) 0.2% (-0.1, 1.4%) 1.6 (0.2 , 14.4) 0.6707

Appendix 7: Analysis of Adjudicated APTC - Study C02-010

Event	Allopurinol	Febuxostat 80	Febuxostat 120	Total
N	**253**	**256**	**251**	**507**
APTC (%)	1 (0.4%)	3 (1.2%)	2 (0.8%)	5 (1.0%)
Diff (95% CI)†		0.8% (-1.1%, 2.7%)	0.4% (-1.0%, 1.8%)	0.6% (-0.9%, 2.0%)
Ratio (95%CI)‡		3.0 (0.3, 28.9)	2.0 (0.2, 22.5)	2.5 (0.3, 21.6)
p-value*		0.6235	0.6228	0.3860
CV Thromboembolic Event (%)	4 (1.6%)	5 (2.0%)	5 (2.0%)	10 (2.0%)
Diff (95% CI)†		0.4% (-2.3%, 3.1%)	0.4% (-1.9%, 2.7%)	0.4% (-1.9%, 2.6%)
Ratio (95%CI)‡		1.2 (0.3, 4.7)	1.3 (0.3, 4.8)	1.3 (0.4, 4.0)
p-value*		>0.999	0.7509	0.7055
All CV events	5 (2.0%)	5 (2.0%)	7 (2.8%)	12 (2.4%)
Diff (95% CI)†		-0.0% (-2.8%, 2.8%	0.8% (-1.9%, 3.5%)	0.4% (-2.1%, 2.9%)
Ratio (95%CI)‡		1.0 (0.3, 3.5)	1.4 (0.4, 4.5)	1.2 (0.4, 3.5)
p-value*		>0.999	0.5752	0.7317
Non-ischemic Event	1 (0.4%)	0	1 (0.4%)	1 (0.2%)
Diff (95% CI)†		-0.4% (-1.6%, 0.8%)	0.0 (-1.1%, 1.1%)	-0.2% (-1.4%, 1.0%)
Ratio (95%CI)‡		0.3 (0.01, 8.1)	1.0 (0.1, 16.2)	0.5 (0.0, 8.0)
p-value*		0.4971	>0.999	0.6158
Non CV Event	3 (1.2%)	3 (1.2%)	2 (0.8%)	5 (1.0%)
Diff (95% CI)†		-0.0% (-2.3%, 2.3%)	-0.4% (-2.1%, 1.3%)	-0.2% (-2.1%, 1.7%)
Ratio (95%CI)‡		1.0 (0.2, 4.9)	0.6 (0.1, 4.0)	0.8 (0.2, 3.5)
p-value*		>0.999	>0.999	0.7996

† difference in proportion between treatment and allopurinol; exact confidence interval based on binomial distribution
‡ continuity correction of 0.5 was used if either treatment group had zero events
* p-value based on Fisher's exact test

Appendix 8: Analysis of Adjudicated APTC – Studies C02-009 and C02-010 (Combined)

Event	Allopurinol	Febuxostat 80	Febuxostat 120	Total
N	521	523	520	1177
APTC (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	1 (0.2%)	4 (0.8%) 0.6% (-0.5%, 1.6%) 4.0 (0.4, 36.0) 0.3738	3 (0.6%) 0.4% (-0.6%, 1.3%) 3.0 (0.3, 29.1) 0.3738	7 (0.6%) 0.4% (-0.3%, 1.1%) 3.1 (0.4, 25.4) 0.2638
CV Thromboembolic Event (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	4 (0.8%)	9 (1.7%) 0.9% (-0.6%, 2.5%) 2.3 (0.7, 7.4) 0.2638	7 (1.4%) 0.6% (-0.9%, 2.0%) 1.8 (0.5, 6.1) 0.3849	16 (1.4%) 0.6% (-0.6%, 1.7%) 1.8 (0.6, 5.4) 0.2975
All CV events Diff (95% CI)† Ratio (95%CI)‡ p-value*	6 (1.2%)	10 (1.9%) 0.8% (-0.9%, 2.4% 1.7 (0.6, 4.6) 0.4510	11 (2.1%) 1.0% (-0.8%, 2.7%) 1.9 (0.7, 5.1) 0.2338	22 (1.9%) 0.7% (-0.6%, 2.1%) 1.6 (0.7, 4.1) 0.2844
Non-ischemic Event Diff (95% CI)† Ratio (95%CI)‡ p-value*	2 (0.4%)	1 (0.2%) -0.2 (-1.0%, 0.7%) 0.5 (0.04, 5.5) 0.6239	2 (0.4%) 0.0 (-1.0%, 1.0%) 1.0 (0.1, 7.1) >0.999	4 (0.3%) -0.0 (-0.8%, 0.7%) 0.9 (0.2, 4.8) 0.8879
Non CV Event Diff (95% CI)† Ratio (95%CI)‡ p-value*	4 (0.8%)	5 (1.0%) 0.2% (-1.1%, 1.5%) 1.2 (0.3, 4.7) >0.999	3 (0.6%) -0.2% (-1.4%, 1.0%) 0.8 (0.2, 3.4) >0.999	9 (0.8%) -0.0 (-1.0%, 1.0%) 1.0 (0.3, 3.2) 0.9946

Appendix 9: Analysis of Adjudicated APTC - Study FGT06-153

Study	Event	Allopurinol	Febuxostat 40	Febuxostat 80	Total
FGT06-153	N	756	757	756	1513
	APTC (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	3 (0.4%)	0 -0.4% (-1.0%, 1.8%) 0.14 (0.0, 2.8) 0.1245	3 (0.4%) 0.0 (-0.8%, 0.8%) 1.0 (0.2, 5.0) >0.999	3 (0.2%) -0.2% (-0.8%, 0.4%) 0.5 (0.1, 2.5) 0.3855
	Non-APTC (%) Diff (95% CI)† Ratio (95%CI)‡ p-value*	7 (0.9%)	10 (1.3%) 0.4% (-0.8%, 1.6%) 1.4 (0.5, 3.8) 0.6271	9 (1.2%) 0.3% (-0.9%, 1.4%) 1.3 (0.5, 3.5) 0.8026	19 (1.3%) 0.3% (-0.7%, 1.3%) 1.4 (0.6, 3.3) 0.4866
	Others Diff (95% CI)† Ratio (95%CI)‡ p-value*	63 (8.3%)	59 (7.8%) -0.1% (-3.4%, 2.3%) 0.9 (0.6, 1.3) 0.7069	51 (6.8%) -1.6% (-4.4%, 1.2%) 0.8 (0.5, 1.2) 0.2839	110 (7.2%) -1.1% (-3.5%, 1.4%) 0.9 (0.6, 1.2) 0.3686

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/s/

Joan Buenconsejo
12/19/2008 04:46:44 PM
BIOMETRICS

Thomas Permutt
12/19/2008 04:48:37 PM
BIOMETRICS
I concur. Dionne Price, team leader, would also have been asked to concur, but she is on leave.

10/12/05

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-856
Drug Name:	Febuxostat (TMX-67) Tablet
Indication(s):	Treatment of Gout
Applicant:	TAP Pharmaceutical Products Inc. 675 N. Field Drive Lake Forest, IL. 60045
Date (s):	Submitted: December 14, 2004
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D. (HFD-725)
Concurring Reviewer:	Thomas J. Permutt, Ph.D. (HFD-715)
Medical Division:	Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)
Clinical Team:	Joel Schiffenbauer, M.D. (HFD-170)
Project Manager:	Jane Dean (HFD-170)
Keywords:	NDA review, Clinical studies

Table of Contents

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this submission the sponsor included reports of two double-blind Phase 3 studies namely, Study #C02-009 and Study #C02-010, and one Phase 2 study namely, Study #C TMX-00-004. The sponsor also submitted report of an open-label safety extension of Studies #C02-009 and #C02-010 under Study #C02-021. At the time of this submission Study #C02-021 was ongoing. Results from an interim analysis of this study were submitted. The length of Study #C02-009 was 28 weeks and that of Study #C02-010 was 52 weeks. The objectives of these studies were to compare the safety and efficacy of some selected doses of febuxostat to allopurinol and placebo for the treatment of subjects with gout.

Since Study #C TMX-00-004 was an inadequately powered short term Phase 2 study and Study #C02-021 was an incomplete open label safety extension study, this reviewer's efficacy conclusion of the study drug was primarily based on Studies #C02-009 and #C02-010. However, results from the other two studies were also considered.

The primary efficacy variable was the proportion of responders, defined as having the last three observed uric acid levels as less than 6.0 mg/dL. Since the length of Study #C02-009 was 28 weeks and that of Study #C02-010 was 52 weeks, for appropriate overall conclusion this reviewer considered data up to 28 weeks from each study. Based on the results from Studies #C02-009 and #C02-010 and also taking the outcomes of Studies #C TMX-00-004 and #C02-021 into account, this reviewer concludes that all doses of febuxostat showed statistically significant difference in efficacy compared to placebo. Results from both studies also demonstrated a superior efficacy of febuxostat 80 mg QD by a superiority margin of 13%, and by more than 13% for other doses.

In this study the reduction of serum urate was considered as a surrogate to the reduction of gout flares. The treatment with all study doses of febuxostat showed highly statistically significant efficacy with respect to the reduction of serum urate. However, results from the secondary efficacy endpoints showed that the percentages of subjects requiring treatment for gout flare in febuxostat groups were not statistically significantly different from that of placebo or allopurinol group. The following table shows the percentages of subjects requiring treatment for gout flares in Studies #C 02-009 and #C 02-010, also percentage of subjects with incidence of gout flare in Study #TMX-00-004.

		Febuxostat				
	Placebo	40 mg	80 mg	120 mg	240 mg	Allopurinol
Study #C 02-009	55%		57%	62%	66%	51%
Study #C 02-010				64%	72%	65%
Study # TMX-00-004	37%	35%				

Therefore, the strength of correlation of this surrogate variable to the reduction of gout flare can be questioned. A clinical judgment is required in this respect.

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Study #C02-009 was a multicenter double-blind, active and placebo-controlled 5-arm study, designed to compare the safety and efficacy of 80, 120 and 240 mgs of febuxostat with 300 mg of allopurinol and placebo in subjects with gout. The study consisted of a washout/run-in period of up to 14 days, a screening visit, and a Day 1 visit for randomization followed by a 28-week double-blind treatment period. Study #C02-010 was a multicenter double-blind, active controlled 3-arm study, designed to compare the safety and efficacy of 80 and 120 mgs of febuxostat with 300 mg of allopurinol in subjects with gout. Similar to Study #C02-009 this study also consisted of a washout of up to 14 days, a screening visit and a Day 1 visit for randomization followed by a 52-week double-blind treatment period. Study #CTMX-00-004 was a Phase 2 multicenter double-blind placebo-controlled 4-arm study, designed to compare the safety and efficacy of 40, 80 and 120 mgs of febuxostat with placebo in subjects with gout. The length of the study was 4-weeks. Study #C02-021 was an open-label extension of Studies #C02-009 and #C02-010. Up to 1500 subjects who had completed these Phase 3 studies were eligible for entry into this long-term extension study. During the study, the site staff was unblinded to the serum urate levels after Visit 2/End of Month 1. At the time of this submission the study was ongoing and expected to continue so that all subjects would have 24 months of treatment. The submitted report is from an interim analysis which was prepared with data contained in the clinical database up to and including 30 April 2004.

1.3 STATISTICAL ISSUES AND FINDINGS

There was no statistical issue that could interfere with the interpretation of the data.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA submission the sponsor included reports of three double-blind Phase 3 studies namely, Study #C02-009, Study #C02-010, and Study #C02-021, and one Phase 2 study namely, Study #CTMX-00-004.

Following are the titles and brief descriptions of the four studies:

Study #C02-009: "A Phase III, Randomized, Multicenter, Allopurinol and Placebo-Controlled Study Assessing the Safety and Efficacy of Oral Febuxostat in Subjects with Gout".

This was a multicenter, randomized, double-blind, parallel-group, dose-response, 5-arm study, designed to compare the safety and efficacy of febuxostat with allopurinol and placebo in subjects with gout. The study consisted of a washout/run-in period that included a screening visit (Day -14 for subjects who were taking allopurinol or uricosuric agents prior to the study; Day -4 for subjects not taking such agents prior to the study), and a Day 1 visit for randomization followed by a 28-week double-blind treatment period. Subjects returned 2 days (Day -2) prior to the Day 1 visit for a complete chemistry panel and serum urate determination. If the subject's serum urate level was $\geq$8.0 mg/dL and the subject continued to meet all other study entry criteria, he/she returned on Day 1 for randomization into the 28-week double-blind treatment period.

Approximately 1000 eligible subjects were randomized in a 1:2:2:1:2 ratio to receive placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, or allopurinol (300 mg QD for subjects with serum creatinine $\leq$1.5 mg/dL on Day -2 and 100 mg QD for subjects with serum

creatinine >1.5 mg/dL and ≤2.0 mg/dL on Day -2). Subjects whose serum creatinine was >2.0 mg/dL at the screening visit, on Day -4, or on Day -2 were not eligible for randomization. Subjects were evaluated at Weeks 2, 4, 6, 8, 12, 16, 20, 24 and 28.

Study #C02-010: "A Phase 3, Randomized, Multicenter Study Comparing the Safety and Efficacy of Oral Febuxostat versus Allopurinol in Subjects with Gout".

This was a Phase 3, multicenter, randomized, double-blind, parallel-group, 3-arm study, conducted to compare the safety and efficacy of febuxostat versus allopurinol in subjects with gout. The design of this study was similar to Study # C02-009 with a treatment period of 52-weeks.

Eligible subjects were randomized in a 1:1:1 ratio to receive febuxostat 80 mg QD, febuxostat 120 mg QD, or allopurinol 300 mg QD. Approximately 250 subjects were randomized to each treatment regimens. Subjects were evaluated at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

Study #CTMX-00-004: "Phase 2, Dose-Response, Safety and Efficacy Study of Oral Febuxostat (TMX-67) in Subjects with Gout".

This was a Phase 2 randomized, double blind, placebo-controlled, parallel-group, multicenter study with a 2-week washout/run-in period and a 4-week treatment period. About 120 male and female subjects were enrolled.

Subjects who were taking allopurinol or uricosuric agents discontinued them at the screening visit. Subjects were washed off of these medications for 2 weeks. Subjects who were not receiving allopurinol or uricosuric agents started a 2-week run-in period prior to randomization in order to begin prophylactic treatment with colchicine. All subjects began treatment with colchicine 0.6 mg BID and continued for 4 weeks, stopping the day before the Day 14 visit (Day 13). The purpose of the colchicine treatment was to decrease the incidence of gout flares during the 2-week washout/run-in period and during the first 2 weeks of the double-blind treatment period.

Qualified subjects with serum urate levels ≥8.0 mg/dL entered the double-blind treatment period and were randomly assigned to 1 of 4 treatment groups namely, placebo, 40, 80, and 120 febuxostat. Double-blind treatment visits occurred on Days 7, 14, 21 and 28. Subjects who completed the 4 week treatment period were given the option of enrolling into a 52-week open-label study of febuxostat.

Study #C02-021: "A Phase 3, Open-Label, Randomized, Allopurinol-Controlled Study to Assess the Long-Term Safety of Oral Febuxostat in Subjects with Gout".

This was a Phase 3, open-label, multicenter, randomized, allopurinol-controlled, 24-month, safety extension of Studies #C02-009 and #C02-010. Up to 1500 subjects who had completed these Phase 3 studies were eligible for entry into this long-term extension study. In this study, the site staff was unblinded to the serum urate levels after Visit 2/End of Month 1.

The original study protocol was for a single-arm study in which all subjects received febuxostat 80 mg QD, with the option to titrate to febuxostat 120 mg QD. However, later an active control arm of allopurinol was added to the study. Subjects were randomized in a 2:2:1 ratio to receive febuxostat 80 mg, febuxostat 120 mg, or allopurinol 300/100 mg once daily. The final visit of Study #C02-009 (Week 28/Visit 13) or Study #C02-010 (Week 52/Visit 17) was considered Day 1 for this study.

2.2 DATA SOURCES

The submission was completely electronic. Submitted study report and data sets were stored in folder \\Cdsesub1\evsprod\n021856\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gout in FDA's Electronic Document Room (EDR).

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY # C02-009

Title: "A Phase III, Randomized, Multicenter, Allopurinol and Placebo-Controlled Study Assessing the Safety and Efficacy of Oral Febuxostat in Subjects with Gout".

3.1.1.1 Design and Objectives

This was a Phase 3, multicenter, randomized, double-blind, allopurinol and placebo-controlled, parallel-group, dose-response, 5-arm study, designed to compare the safety and efficacy of febuxostat versus placebo and allopurinol in subjects with gout. The study consisted of a Washout/ Run-in period that included a screening visit (Day -14 for subjects who were taking allopurinol or uricosuric agents prior to the study or Day -4 for subjects not taking such agents prior to the study), a Day -4 visit for subjects whose screening visit occurred on Day -14. All subjects returned 2 days (Day -2) prior to the Day 1 randomization visit for a complete chemistry panel and serum urate determination. If the subject's serum urate level was ≥8.0 mg/dL as determined by the central laboratory, and the subject continued to meet all other study entry criteria, the subject returned on Day 1 for randomization into the 28-week double-blind treatment period.

Approximately 1000 eligible subjects were to be randomized in a 1:2:2:1:2 ratio to receive placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, or allopurinol (300 mg QD for subjects with serum creatinine ≤1.5 mg/dL on Day -2 and 100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤2.0 mg/dL on Day -2). Subjects whose serum creatinine was >2.0 mg/dL at the screening visit, on Day -4, or on Day -2 were not eligible for randomization.

Following randomization, subjects returned to the site for study visits that were conducted in the morning at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28. Subjects who completed the 28-week double-blind treatment period were given the option of enrolling in a 24-month, long-term, open-label study of febuxostat and allopurinol (Study #C02-021).

The objective of this study was to compare the safety and efficacy of different oral doses of febuxostat versus placebo and allopurinol in subjects with gout.

3.1.1.2 Primary Efficacy Endpoint

The primary efficacy variable was the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.

3.1.1.3 Secondary Efficacy endpoint

Secondary efficacy variables included:

- The proportion of subjects whose serum urate levels were <6.0 mg/dL.
- The percent reduction in serum urate levels.

- The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at the screening visit.
- The reduction in the total number of tophi in the subset of subjects with palpable tophi at the screening visit.
- The proportion of subjects requiring treatment for a gout flare between Weeks 8 and 28 of the 28-week double-blind treatment period.

3.1.1.4 Patients Analyzed

Intent-to-Treat (ITT) Population: The ITT population was defined as all randomized subjects who received at least one dose of study drug and had serum urate levels ≥8.0 mg/dL at the last visit prior to Day 1 as determined by the central laboratory.

Safety Population: All randomized subjects who received at least one dose of study drug were included in the safety analyses.

3.1.1.5 Disposition of Patients, Demography, and Baseline characteristics

Disposition of subjects, and demographic and baseline characteristics are shown in Tables 1 and 2 in the appendix. One thousand seventy-two subjects were randomized and received at least one dose of study drug. Table 1 shows 134 subjects received placebo, 267 received febuxostat 80 mg QD, 269 received febuxostat 120 mg QD, 134 received febuxostat 240 mg QD, and 268 received allopurinol 300/100 mg QD. Results from subjects receiving either allopurinol 100 mg QD (n=10) or 300 mg QD (n=258) were summarized together in all statistical tables.

A clinical site closure due to GCP (good clinical practice) noncompliance occurred at Site #18032. A letter regarding this closure was submitted to the FDA on 12 May 2004, which indicated that the data for the 2 subjects enrolled at the site [4115 (febuxostat 80 mg QD) and 4123 (allopurinol 300 mg QD)] would be excluded from the clinical trial database. Review of the data revealed that both were non-responders in the primary efficacy analysis and neither of these subjects experienced adverse events or gout flares. Laboratory data were available for these two subjects, therefore a decision was made upon consultation with the FDA to include these data in the database for efficacy and safety analyses.

Overall, 28% (300/1072) of the subjects prematurely discontinued treatment; 33 (25%) subjects discontinued from the placebo group, 93 (35%) subjects discontinued from the febuxostat 80 mg QD group, 69 (26%) subjects discontinued from the febuxostat 120 mg QD group, 48 (36%) subjects discontinued from the febuxostat 240 mg QD group, and 57 (21%) subjects discontinued from the allopurinol 300/100 mg QD group. Of the subjects who prematurely discontinued from the study, 63% (188/300) discontinued within the first 12 weeks, and discontinuation rates declined thereafter. The percentage of subjects who prematurely discontinued within the first 12 weeks was comparable across the treatment groups (58% to 69%). The most frequent primary reason for discontinuing study drug, was lost to follow-up (24%, 72 subjects). A greater proportion of subjects in the febuxostat 80 mg QD, febuxostat 120 mg QD, and febuxostat 240 mg QD treatment groups prematurely discontinued treatment due to gout flare (14%, 9%, and 17%, respectively) compared to the placebo and allopurinol 300/100 mg QD (0% and 2%, respectively) treatment groups. Thirty-seven subjects discontinued from the study due to a primary reason of "other"; withdrawal of consent (19 subjects) and noncompliance (13 subjects) were the most frequently reported "other" reasons for discontinuation.

Overall, subjects ranged from 22 to 84 years in age. The mean age ranged from 50.6 to 54.3 years among all treatment groups. The majority of the study population was Caucasian (78%) and most subjects were male (94%). The majority of subjects reported the use of alcohol (66%) and were non-/ex-tobacco users (80%). The mean BMI for all subjects was 32.7 kg/m2 and 62% had a BMI of ≥30 kg/m2. Among all subjects, there were no statistically significant differences among the treatment groups in gender, race, age, height, tobacco use, alcohol use, or BMI. A statistically significant difference was observed among the treatment groups in weight, with a lower mean weight in the placebo group (215.2 pounds) compared to the febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups (227.6, 230.3, 227.2, and 224.1 pounds, respectively).

3.1.1.6 Sample size determination and Efficacy Analysis

3.1.1.6.1 Determination of sample size

A total of 1000 subjects (125 subjects in each of the placebo and febuxostat 240 mg QD treatment groups and 250 subjects in each of the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups) were planned to be enrolled into this study. This sample size was to provide: 1) at least 95% power to detect a difference of at least 45% between each of the febuxostat treatment groups and placebo for the primary efficacy variable; 2) at least 80% power to meet the non-inferiority criteria between at least one febuxostat treatment group and the allopurinol 300/100 mg QD treatment group for the primary efficacy variable; and 3) at least 90% power to detect a 15% difference between a febuxostat treatment group and the allopurinol 300/100 mg QD treatment group for the primary efficacy variable. Since the febuxostat 240 mg QD treatment group was included in this study to establish the safety profile of a dose that was twice the anticipated maximum clinical dose of 120 mg QD, the power of comparisons between the febuxostat 240 mg QD treatment group and the allopurinol treatment group was not considered. Therefore, an unequal randomization was chosen for this study in which subjects were randomly assigned in a 1:2:2:1:2 ratio to receive placebo, febuxostat 80 mg, 120 mg, 240 mg, and allopurinol 300/100 mg.

3.1.1.6.2 Efficacy Analysis

The comparisons for the primary efficacy variable were done sequentially using the following 3 steps:

1. Each febuxostat treatment group was compared to the placebo group with a CMH test stratified by baseline renal function. Superiority of a febuxostat treatment group to the placebo group was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's method, described below. If each dose of febuxostat was shown to be superior to placebo, the procedure proceeded to Step 2.

2. Binomial 97.5% confidence intervals, based on the normal approximation for the binomial distribution, were calculated for the differences in response rates between each treatment group of febuxostat (80 mg QD and 120 mg QD) and the allopurinol 300/100 mg QD treatment group. Non-inferiority to allopurinol was declared if the absolute value of the lower bound of the 97.5% confidence interval did not exceed 10%.

3. Each febuxostat treatment group that was shown to be non-inferior to allopurinol in Step 2 was compared to the allopurinol 300/100 mg QD treatment group to test for superiority. The test for superiority was performed using a CMH test stratified by baseline renal function. If both treatment groups of febuxostat were compared to allopurinol, superiority of a febuxostat treatment group to

the allopurinol 300/100 mg QD treatment group was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's method and the response rate for the febuxostat treatment group was higher than that for the allopurinol 300/100 mg QD treatment group. If only 1 treatment group of febuxostat was compared to allopurinol, superiority of the febuxostat treatment group to the allopurinol 300/100 mg QD treatment group was declared if the p-value from the CMH test was ≤ 0.05.

In the Hochberg's method in steps 1 and 3, the p-values from the pairwise comparisons were ordered from smallest to largest. The largest p-value was compared to 0.05. If the largest p-value was less than or equal to 0.05, all the comparisons were considered statistically significant. If the largest p-value was greater than 0.05, then the comparison corresponding to that p-value was not considered statistically significant. The second largest p-value was then compared to 0.05/2=0.025. If the second largest p-value was less than or equal to 0.025, then all the remaining comparisons were considered statistically significant. If the second largest p-value was greater than 0.025, then the comparison corresponding to that p-value was not considered statistically significant. The third largest p-value was then compared to 0.05/3=0.017 (only in step 1 if applicable) and if it was less than or equal to 0.017, the corresponding comparison was considered statistically significant.

Additionally, comparisons were made between the febuxostat 240 mg QD and allopurinol groups, between the allopurinol and placebo group, and between the febuxostat treatment groups using a CMH test stratified by baseline renal function. No adjustment to the alpha level was made for these comparisons.

For the secondary efficacy variables pairwise comparisons were made between the treatment groups. No adjustments for multiple comparisons were performed.

No interim analyses were performed.

3.1.1.6.3 Handling of dropouts or missing data

In order to be considered a responder in the primary efficacy analysis, each of a subject's last 3 serum urate levels must have been <6.0 mg/dL. If a subject prematurely discontinued from the study before at least 3 serum urate levels were obtained, the subject was considered a non-responder. A sensitivity analysis was conducted for the primary efficacy variable by using the available (1 or 2) serum urate levels to determine response for subjects who prematurely discontinued before at least 3 serum urate levels were obtained. This analysis examined the effect of assigning these subjects as non-responders in the primary analysis. Subjects without post-baseline serum urate levels were not included in this analysis. For all primary and secondary efficacy analyses, missing data were not imputed.

With regard to QOL questionnaires, missing data for the SF-36 health survey were handled using techniques provided in the SF-36 analysis guidelines. Furthermore, values for missing 6-point MOS health distress items were imputed using the mean of the available items if at least 2 of the 4 items were available. Missing data for the GAQ were not imputed. If a response to the Minnesota Living with Heart Failure Questionnaire was missing after baseline data had been collected, the baseline value was assigned to the missing response; if a response to a question was missing at baseline, a zero was assigned to that question at both baseline and post-baseline time points.

3.1.1.6.4 Multiple centers

This study was performed at 167 investigational sites. Investigational site was not used as a factor in the statistical analysis. No site enrolled more than 3% of all subjects, so it was not expected that individual sites would have a large effect on the overall results. Data were not summarized by center due to small numbers of subjects in each treatment group at most sites.

3.1.1.7 Sponsor's Results and Conclusions

3.1.1.7.1 Primary efficacy outcome

Text Table 1 shows the sponsor's analysis results. The sponsor's results show that the proportions of ITT subjects whose last 3 serum urate levels were <6.0 mg/dL were 0%, 48%, 65%, 69%, and 22% in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD groups, respectively. Efficacy of each of the febuxostat treatment groups and the allopurinol 300/100 mg QD treatment group was statistically significantly different from placebo. The lower 97.5% confidence limits on the differences of percentage of responders between febuxostat 80 mg QD and allopurinol 300/100 mg QD, and 120 mg QD and allopurinol 300/100 mg QD were 17% and 34%, demonstrating superiority of febuxostat 80 mg QD by a superiority margin of 17 % and by 34% for febuxostat 120 mg QD. Furthermore, the difference between the febuxostat 80 mg QD treatment group and each of the other febuxostat treatment groups was statistically significant. The difference between the febuxostat 120 mg QD and 240 mg QD treatment groups was not statistically significant.

Text Table 1
Summary of Responders - ITT Subjects
Study #C 02-009

Last 3 Serum Urate Levels <6.0 mg/dL	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Yes	0/134 (0%)	126/262 (48%)[a,b,c]	175/269 (65%)[a]	92/134 (69%)[a,b]	60/268 (22%)[a]
No	134/134 (100%)	136/262 (52%)	94/269 (35%)	42/134 (31%)	208/268 (78%)

	Difference in Proportions	97.5% CI[†]	P-value[‡]
Febuxostat 80 mg vs. Allopurinol 300/100 mg	26%	(16.7%, 34.7%)	<0.001[c]
Febuxostat 120 mg vs. Allopurinol 300/100 mg	43%	(34.0%, 51.3%)	<0.001[c]

† 97.5% CI = 97.5% confidence interval for the difference in proportions based on the normal approximation for the Binomial distribution
‡ P-values from a CMH test stratified by baseline renal function (serum creatinine ≤1.5 mg/dL vs. >1.5 mg/dL)
Source: Table 11.4a of sponsor's analysis

A sensitivity analysis was conducted for the primary efficacy variable by using the available (1 or 2) serum urate levels to determine response for subjects who prematurely discontinued before at least 3 serum urate levels were obtained. In the primary analysis, these subjects were assigned as non-responders since they did not have at least 3 serum urate levels. Table 3 in the appendix shows the results. The proportions of subjects whose last 3 serum urate levels were <6.0 mg/dL were slightly higher in this sensitivity analysis compared to the overall analysis. Among ITT subjects, response rates were 0%, 57%, 70%, 83%, and 25% in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively. The differences between each of the active treatment groups and the placebo group were statistically significant ($p<0.001$). The lower 97.5% confidence limits on the differences of percentage of

responders between febuxostat 80 mg QD and allopurinol 300/100 mg QD, and 120 mg QD and allopurinol 300/100 mg QD were 23% and 37%, demonstrating superiority of febuxostat 80 mg QD relative to allopurinol by a superiority margin of 23% and by 37% for febuxostat 120 mg QD. The proportions of responders were analyzed by baseline serum creatinine and baseline serum urate levels. The results are shown in Tables 4 and 5 in the appendix. Each sub-group showed statistically significant difference in response rates between febuxostat doses and placebo.

3.1.1.7.2 Secondary Efficacy outcomes

The following are the sponsor's findings regarding secondary efficacy outcomes.

Proportion of Subjects Whose Serum Urate Levels were <6.0 mg/dL at Each Visit

The proportions of subjects whose serum urate levels were <6.0 mg/dL were statistically significantly greater in each of the febuxostat groups compared to the allopurinol 300/100 mg QD group and in each of the active treatment groups compared to the placebo group at the Week 28 and Final Visits. Furthermore, the majority of pairwise comparisons of response rates in the febuxostat groups were statistically significant, with response rates increasing with dose. The reduction in serum urate levels to <6.0 mg/dL was observed in all treatment groups at the Week 2 Visit and was maintained throughout treatment. Throughout the course of the study, response rates ranged from 0% to 1%, 69% to 80%, 79% to 89%, 85% to 98%, and 35% to 41% in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively.

Percent Reduction in Serum Urate Levels

The mean percent change from baseline in serum urate levels was statistically significantly different between each of the febuxostat groups and the allopurinol 300/100 mg QD treatment group and between each active treatment group and the placebo group at the Week 28 and final visits, with smaller mean decreases observed in the placebo and allopurinol 300/100 mg QD groups. Furthermore, all pairwise comparisons of febuxostat groups with respect to percent reduction in serum urate levels at the Week 28 and final visits were statistically significant, with the reduction increasing with dose. The percent reduction in serum urate levels was observed in all treatment groups at the Week 2 visit and was maintained throughout treatment.

Throughout the course of the study, mean percent changes from baseline ranged from +2% to -4%, -45% to -50%, -52% to -56%, -65% to -70%, and -33% to -34% in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively.

Percent Reduction in Primary Tophus Size Determined by Physical Measurement Among Subjects with a Primary Palpable Tophus at Baseline

Among subjects with a primary palpable tophus at baseline, there were no statistically significant differences between treatment groups for the percent change from baseline in primary tophus size at the Week 28 or final visits. In each treatment group, there was a trend toward larger median percent changes from baseline over time. The median percent change from baseline at Week 28 was -52.0%, -45.6%, -54.2%, -53.2%, and -31.5% in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively.

Percent Reduction in Primary Tophus Size Excluding Elbow Locations Determined by Physical Measurement Among Subjects with a Primary Palpable Tophus at Baseline

Change in tophus size was evaluated excluding elbow tophi due to the variability in measurements occurring at that anatomical site, which may be due to olecranon bursal fluid. Among subjects with a primary palpable tophus at baseline, the percent change from baseline in primary tophus size (excluding elbow locations) was statistically significantly different between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups at the Week 28 and final visits. Subjects in the febuxostat 120 mg QD group had greater percent decreases from baseline in primary tophus size compared to the allopurinol 300/100 mg QD treatment group at the Week 28 and final visits. The median percent change from baseline at Week 28 was -39.6%, -33.2%, -56.7%, -44.3%, and -16.1% in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively.

Percent Reduction in Primary Tophus Size by Average Post-baseline Serum Urate Level Among Subjects with a Primary Palpable Tophus at Baseline

Among subjects with a primary palpable tophus at baseline, the median percent change from baseline in primary tophus size was numerically greater in the group that achieved an average post-baseline serum urate level <6.0 mg/dL compared to the group that achieved an average post-baseline serum urate level ≥6.0 mg/dL. At Week 28, the median percent change from baseline in primary tophus size was -51.4% in the group of subjects that achieved an average post-baseline serum urate level <6.0 mg/dL compared to –39.0% in the group of subjects that achieved an average post-baseline serum urate level ≥6.0 mg/dL.

Reduction in Total Number of Tophi Among Subjects with Palpable Tophi at Screening

With the exception of the difference between febuxostat 120 mg QD and placebo at Week 28, no statistically significant differences were observed between treatment groups in the change from baseline in number of tophi at the Week 28 and final visits among subjects with palpable tophi at baseline. In each treatment group, there was little change in median values over time. A decrease in the mean number of tophi was noted over time in each treatment group and the mean change from baseline at Week 28 was -0.3, -0.3, -1.2, -0.4, and -0.4 tophi in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively.

Proportion of Subjects Requiring Treatment for a Gout Flare

The majority of subjects in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups received treatment for a gout flare during the study (55%, 57%, 62%, 66%, and 51%, respectively). The proportion of subjects requiring treatment for a gout flare was similar across the treatment groups (7% to 10%) during the screening period before study drug had been started. Double-blind Treatment Period (Day 1 to Week 28), a statistically significantly greater proportion of subjects in each of the febuxostat 120 mg QD (62%) and 240 mg QD (66%) treatment groups required treatment for a gout flare compared to the allopurinol 300/100 mg QD treatment group (51%).

Quality-of-life Results

Short Form-36 Health Survey

Statistically significantly greater improvements compared to placebo were observed in the febuxostat 80 mg QD and 240 mg QD treatment groups at the Week 28 Visit in Role-Physical. Statistically significantly greater improvements compared to placebo were observed in reported health transition at Week 28 (febuxostat 240 mg QD) and the final visit (febuxostat 120 mg QD). The placebo group had statistically significantly greater improvements at the final visit in physical functioning compared to the febuxostat 80 mg QD treatment group and in mental health compared to the febuxostat 240 mg QD treatment group).

Medical Outcomes Study Health Distress Scale

There was statistically significant improvement over time in each treatment group for the MOS health distress scale. There were no statistically significant differences between the treatment groups at the final visit in MOS health distress. The febuxostat 80 mg QD group had a statistically significantly greater improvement than the allopurinol 300/100 mg QD treatment group at the Week 28 visit in the MOS health distress scale.

Gout Assessment Questionnaire

The allopurinol 300/100 mg QD treatment group had statistically significantly greater improvements than the febuxostat 120 mg QD treatment group in productivity and had a statistically significantly greater mean value (less bothered) for treatment bother than the febuxostat 240 mg QD treatment group at the Week 28 visit. Additionally, the allopurinol 300/100 mg QD treatment group had statistically significantly greater improvement than the febuxostat 80 mg QD treatment group in gout concern and than the febuxostat 80 mg QD and 120 mg QD treatment groups in well-being at the final visit. The allopurinol 300/100 mg QD treatment group also had statistically significantly greater mean values for treatment bother (less bothered) than the febuxostat 240 mg QD treatment group and for treatment satisfaction (more satisfaction) than the febuxostat 80 mg QD and 240 mg QD treatment groups at the final visit. Allopurinol 300/100 mg QD-treated subjects had statistically significantly greater improvements than febuxostat 80 mg QD- and 120 mg QD-treated subjects in gout flare symptom interference and each of the febuxostat treatment groups in productivity at the final visit. The placebo group had statistically significantly greater improvements than the febuxostat 80 mg QD treatment group in gout concern, than the febuxostat 120 mg QD treatment group in productivity, and than the febuxostat 80 mg QD and 120 mg QD treatment groups in gout flare symptom interference and well-being at the Week 28 visit. Additionally, the placebo group had statistically significantly greater improvements than the febuxostat 80 mg QD and 120 mg QD treatment groups at the final visit in well-being, than the febuxostat 80 mg QD treatment group in Gout Concern, and than each of the febuxostat treatment groups in gout flare symptom interference, productivity, and hours unable to leave home. The placebo group also had a statistically significantly greater mean value (less bothered) for treatment bother than the febuxostat 240 mg QD treatment group at the final visit. Additionally, statistically significant differences between febuxostat treatment groups were observed for gout concern and treatment bother. There were no statistically significant differences between treatment groups for the gout pain and severity, treatment convenience, and hours unable to work scales.

11.4.1.3.4 Minnesota Living With Heart Failure Questionnaire

The numbers of subjects who completed the Minnesota Living with Heart Failure Questionnaire were fewer than 10 per treatment group, so it is difficult to interpret the results with any confidence. The allopurinol 300/100 mg QD treatment group showed a mean increase of 21 and 19 points at Week 28 and the final visit, respectively. In the physical dimension score, the placebo group showed a slight mean decrease at Week 28, but a slight mean increase at the final visit. The febuxostat 80 mg QD and 240 mg QD treatment groups showed slight mean decreases at both Week 28 and the final visit. The febuxostat 120 mg QD treatment group was essentially unchanged at Week 28 and the final visit, while the allopurinol 300/100 mg QD treatment group showed a 10 to 12 point mean increase at Week 28 and the final visit. The placebo, febuxostat 120 mg QD, and febuxostat 240 mg QD treatment groups showed slight mean decreases in the emotional dimension score at Week 28 and the final visit, while the febuxostat 80 mg QD treatment group was essentially unchanged at both visits and the allopurinol 300/100 mg QD treatment group showed slight mean increases at both visits.

3.1.1.8 Reviewer's Findings and Conclusions

To verify the sponsor's analysis this reviewer reanalyzed the primary efficacy variable. The length of the study was designed for 28 weeks. However, double blind observations were submitted for up to 39 weeks. In this review this reviewer analyzed the data of all patients with observations up to 28 weeks as the primary analysis. In addition, to evaluate the for sensitivity of the analysis this reviewer also analyzed the data of all patients with all observations and 28 weeks completers with observations up to 28 weeks. Text Table 2 shows this reviewer's analysis.

Text Table 2
***P-values Comparing Responders in Febuxostat and Placebo and 97.5% Confidence Intervals on difference of Percentage of Responders Between Febuxostat and Allopurinol**
Study # C 02-009

Population	Treatment	N	Responder	Percent	97.5 % C. I.
All patients All observations	FEBUXOSTAT 240 MG QD	134	85	63	30 - 53
	FEBUXOSTAT 120 MG QD	269	164	61	30 - 48
	FEBUXOSTAT 80 MG QD	267	119	45	14 - 32
	ALLOPURINOL 300/100 MG QD	268	58	22	
	PLACEBO	134	1	1	
All patients Observations up to Week 28 regardless if patients completed 28 weeks	FEBUXOSTAT 240 MG QD	134	87	65	31 - 54
	FEBUXOSTAT 120 MG QD	269	170	63	31 - 50
	FEBUXOSTAT 80 MG QD	267	121	45	13 - 32
	ALLOPURINOL 300/100 MG QD	268	61	24	
	PLACEBO	134	0	0	
28 weeks completers Observations up to 28 weeks	FEBUXOSTAT 240 MG QD	86	70	81	42 - 67
	FEBUXOSTAT 120 MG QD	201	146	73	35 - 56
	FEBUXOSTAT 80 MG QD	175	102	58	20 - 43
	ALLOPURINOL 300/100 MG QD	212	57	28	
	PLACEBO	101	1	1	

*** All p-values comparing febuxostat and allopurinol or comparing febuxostat and placebo were <0.0001.**